Wake Up Narcolepsy Impact Statement (updated 9/2024)

The mission of Wake Up Narcolepsy (WUN) is to drive Narcolepsy awareness, education and research towards improved treatments and a cure.

In line with our mission, we believe efforts in scientific research will lead to development of improved treatments as well as a cure for narcolepsy. Over the last several years we have funded basic and clinical researchers to further these efforts. We discuss some of them below. Our funds have led to novel findings of the genetic influence on susceptibility or protection, as well as brain regions involved with narcolepsy. Our funds have also facilitated the generation of important tools in the diagnosis of narcolepsy.

WUN has funded Dr. Emmanuel Mignot of Stanford University who has made marked progress in identifying genetic markers of risk and protection from narcolepsy (Mignot 2013, 2015a, 2015b). His research creates avenues to the development of diagnostic and predictive assays for the disease, as well as the potential for "immunization" against narcolepsy.

WUN has funded Dr. Thomas Scammell of Harvard Medical School and BIDMC which led to the discovery that there is an increased number of neurons that release histamine in the brain of people with narcolepsy (Scammell 2013). This novel observation led to investigation of whether a drug that targets the histamine system, Pitolisant, would promote wake in people with narcolepsy. Since 2019 in the US, and 2016 in the EU, Pitolisant has been readily prescribed for narcolepsy with high efficacy in improving wakefulness and reducing cataplexy.

Cataplexy is ranked as one of the most disruptive symptoms of narcolepsy. We have funded multiple researchers who are pursuing the basic understanding of the neuronal circuits involved in the generation of cataplexy (Peever 2017 & Scammell 2017). We have a better understanding of how emotions and social interactions may trigger cataplexy. These findings will inform the pursuit of pharmacological approaches to reduce cataplexy.

We have supported clinical researchers to better understand the impact of narcolepsy and the effectiveness of current treatments. In fact, the FDA-led patient focused drug development (PFDD) held in 2013 was the only of its kind to have a scientific paper (Maski 2017). This was possible due to our support of Dr. Kiran Maski of Boston Children's Hospital. Her research highlighted the need for better diagnostic tools for the pediatric population and more educational resources to address a significant delay among patients with pediatric onset of symptoms. Her results showcased a broader range of symptoms that negatively impact and limit the activities in which they engage. Wake Up Narcolepsy has continued to fund clinical research aimed to develop novel markers of narcolepsy and idiopathic hypersomnia in children and to reduce the delay in diagnosis (Maski 2022, Malow 2010, 2017, Ong 2020a, 2020b, Narang 2018, 2019, 2020, Ingram 2021a, 2021b).

"WUN aims to continue fundraising in order to accelerate narcolepsy research. More work needs to be done to understand how orexin/hypocretin cells are dying in the brain and whether an autoimmune process underlies the origin of narcolepsy for a majority of cases. Are there novel targets of pharmacological approaches to reduce symptom severity and lessen the impact narcolepsy has on activities of everyday life? Are the tools developed thus far for diagnosing narcolepsy, properly and

widely used? These and other questions require our continued support and advocacy to achieve WUN's mission," reports Monica Gow, Co-Founder and Executive Director of Wake Up Narcolepsy.

Maximizing WUN funding to accelerate narcolepsy research

WUN aims to continue fundraising to accelerate transformative discoveries from narcolepsy research. Substantial advancements in understanding the causes, new treatments for and impact of narcolepsy requires large amounts of money. There are significant roadblocks to acquiring federal funding for investigating narcolepsy. We highlight below some challenges researchers must address to acquire large federal funding for narcolepsy research. WUN aims to develop mechanisms to help support research and to increase the impact of our fundraising. For example, WUN has teamed with the American Academy of Sleep Medicine Foundation to jointly fund research in understanding central disorders of hypersomnolence. This triples the impact of each WUN dollar toward research of sleep disorders and increases our exposure among clinicians and researchers.

Top reasons funding for sleep disorder research is difficult.

Most sleep research is complicated and expensive, requiring large monetary NIH grants. However, these grants are very competitive. NIH budget cuts have reduced the funds available for grants and therefore reduced the number of grants funded each cycle. Furthermore, the NIH generally does not fund exploratory research, but this early-stage research is often the path toward genuinely novel advances.

Importance of preliminary data.

To demonstrate the likely success of an experiment, many larger grant proposals require preliminary data. Applications that include preliminary data receive better reviews and are more likely to receive funding. Pilot experiments, those small-scale experiments designed to demonstrate the likelihood of success, require $100,000 or more, for up to two years to generate sufficient preliminary data.

WUN funding translates into larger federal grants and publications.

WUN funding supports the development of novel ideas. Below are a few examples:

1. In the Scammell lab, WUN funding was used to support the efforts of one postdoctoral fellow to generate pilot data used to obtain a $1.5 million grant from the NIH. This project highlights the role of social interaction and cataplexy. Specifically, neurons that promote social behavior, also increase the likelihood of cataplexy, in a mouse model of narcolepsy. Results from this project are in review in a top-tier science journal, Nature Neuroscience.
2. In the Maski lab, WUN funds supported the development of a hypersomnia data repository. Pilot data collected from this repository was then used to obtain a multi-year R61/R33 grant sponsored by the National Institutes of Health/National Institute of Neurological Disorders and Stroke (awarded in June 2024). ~$500,000 in direct costs for 2024
3. Dr. Peever, University of Toronto, has had publication success with support from WUN. Two recent manuscripts from the Peever lab are a direct result of WUN funding (PMID: 37044089 and one in review at Current Biology). The first publication presents their findings that grafting orexin cells into the brain of narcoleptic mice restores motor behavior and prevents cataplexy.

Although funds from WUN may account for less than 10% of a large lab's overall research costs, WUN funding provides much-needed flexibility and the opportunity to pursue new, higher-risk questions. WUN is committed to developing additional mechanisms through partnerships to maximize WUN's fundraising toward research support.

The following sections are designed to highlight responses from the PIs and give some quick facts about the impact of WUN funding.
Statements from the PIs:

David Ingrahm: We have been very grateful for the support and services that Wake Up Narcolepsy provides. In terms of research support, their funding allowed us to perform a study of narcolepsy in children to help identify challenges, including psychosocial and medical comorbidities (PMID: 32895119), as well as, evaluate relative effectiveness of treatment approaches and care delivery for children with narcolepsy (PMID: 33283753). Beyond research, the organization provides important services for families and patients, such as education day events and support groups.

Quick reference to articles PMID: 32895119, 33283753

Indra Narang: The Money from WUN has been used to conduct both qualitative and quantitative research in Toronto and more specifically, the money has been/is used to pay for research personnel to conduct the research. The money is also being used for a collaborative research project with Dr. Kiran Maski at Boston Children's hospital.

PMID: 33877929, 32651734, 31844391, 31070768, 30455579

Kiran Maski: Our research group endeavors to improve timely diagnosis of pediatric narcolepsy. With WUN support, we developed and validated the Pediatric Hypersomnolence Survey now published in the journal Neurology https://pubmed.ncbi.nlm.nih.gov/35314496/. We hope this survey can be used in healthcare settings and the community to more quickly identify children and adolescents with potential narcolepsy or idiopathic hypersomnia for more directed expert referrals and appropriate diagnostic testing.

PMID: 35314496, 27923434

Tom Scammell: Our research group focuses on understanding the brain mechanisms of narcolepsy, from the roles of specific types of neurons to how these cells work together to produce sleepiness and cataplexy. Funding from WUN has supported research on how loss of the orexin/hypocretin neurons in people with narcolepsy can increase the number of neurons making histamine. Using mouse models of narcolepsy, the lab has also studied the functions of these histamine-producing neurons; how the age of narcolepsy onset may relate to severity of symptoms; the role of the amygdala in emotion-triggered cataplexy; and how oxytocin contributes to the occurrence of cataplexy in social circumstances. This flexible funding from WUN enabled Dr. Scammell to obtain pilot data that was instrumental in obtaining large NIH research grants and complete high impact experiments.

PMID: 23904672, 24006291, 28235898, 32249922, 33746708

Emmanuel Mignot: Dr. Emmanuel Mignot and his research team have completed Genome Wide Association studies to uncover why narcolepsy develops in some individuals but not others. This includes populations that received the Pandemrix vaccine. Additionally, the research team generated a computer program to screen more patients in a more efficient manner than the MSLT by identifying 5 predictive markers of narcolepsy.

PMID: 25574827, 24204295, 25452148, 26299470, 26611950, 30523329, **37188663**

John Peever: WUN funding has allowed me to support, in part, 2 PhD students whose research is focused on mechanisms of cataplexy in narcolepsy. WUN funding has allowed us to publish 2 papers (Current Biology and The Neuroscientist).
PMID: 31679942, 34704497, 28209737, **37044089**

Beth Malow: Thank you again for your generosity in wanting to support our research on narcolepsy. We are excited about partnering with your foundation!

PMID: 29117887, 20191943

Jason Ong: We greatly appreciate the support from WUN, which has allowed us to carry out and complete these projects during the pandemic. We hope that our work will provide evidence-based strategies using digital and tele-health delivery to improve the mental health and quality of life among people with narcolepsy.

PMID: 31937147, 32804069

Ariel Neikrug: Dr. Neikrug recently received funds from WUN and aims to address how the behavioral pattern of day-to-day life is impacted by narcolepsy. Dr. Neikrug wrote “With the money from Wake-Up Narcolepsy we will be able to utilize existing data for Behavioral activity rhythms characterization and to set the stage and yield preliminary data that will then support future NIH-funded research.”

Wake Up Narcolepsy Bullet points

Total amount of money funding research since 2008: $1.39 million

# of researchers funded: _11_

Institutions represented:

AASM Foundation
Beth Israel Deaconess Medical Center and Harvard Medical School
Boston Children's Hospital and Harvard Medical School
Northwestern University/Feinberg School of Medicine
Stanford University/ Stanford Center for Sleep Sciences and Medicine
The Hospital for Sick Children (SickKids)
University of California-Irvine
University of Michigan
University of Missouri-Kansas City
University of Toronto
Vanderbilt University Medical Center

# of publications acknowledging WUN or with confirmation funds were used to support the research:

27

Impact Factor by journal WUN funded researchers have published in:

17.69 Nature Communications
10.83 Current Biology (Peever)
10.42 Annals of Neurology (Scammell)
9.901 Neurology (by American Academy of Neurology) (Maski)
7.519 The Neuroscientist (Peever)
6.167 The Journal of Neuroscience (Peever, Scammell)
5.917 PLoS Genetics (Mignot)
5.85 Sleep (Narang, Scammell(2))
5.061 Current Neurol Neuroscience Rep (Narang (2))
3.586 Journal of Clinical Sleep Medicine (Maski, Malow(2), Ingram(2), Ong)
3.566 Frontiers in Neuroscience (Scammell)
3.171 Behavioral Sleep Medicine (Ong, Narang)
1.979 Child Health (Narang)

Researchers and their current institution and contact information:

David G. Ingram, MD
Associate Professor
Department(s) of Pediatrics
Section: Pulmonology and Sleep Medicine
Children's Mercy Hospital
University of Missouri-Kansas City
dgingram@cmh.edu

Beth Ann Malow, MD
Vice Chair Academic Affairs
Division Chief Sleep
Professor Neurology
Vanderbilt University Medical Center
1211 Medical Center Drive, Nashville, TN 37232
(615) 322-5000
beth.malow@Vanderbilt.Edu

John H. Peever, PhD
Professor
Centre for Biological Timing and Cognition
Department of Cell & Systems Biology
University of Toronto
325 Huron Street
Toronto, Ontario, Canada
M5S 3G3
416-946-5564
john.peever@utoronto.ca

Thomas E. Scammell, MD
Harvard Medical Faculty Physicians
Neurology, Sleep Medicine
BIDMC Department of Neurology
Sleep Studies
330 Brookline Avenue
Boston, MA 02215-5400
(617) 667-3237
tscammel@bidmc.harvard.edu

Kiran Maski, MD
Assistant Professor of Neurology
Department of Neurology, Boston Children's Hospital
Children's Hospital
Peabody Satellite
300 Longwood Ave
Boston, MA 02115
Kiran.Maski@childrens.harvard.edu

Emmanuel Mignot, MD, PhD
CRAIG REYNOLDS PROFESSOR OF SLEEP MEDICINE AND PROFESSOR, BY COURTESY, OF GENETICS AND OF NEUROLOGY
University - Faculty
Department: Psych/Sleep Medicine
Position: Professor
Stanford Center for Sleep Sciences and Medicine
3165 Porter Drive
Palo Alto, California 94304
(650) 725-6517 (office)
*Paige Collazo - Administrative Assistant
*Email pcollazo@stanford.edu

Jason Ong, PhD
Adjunct Associate Professor of Neurology (Sleep Medicine)
Northwestern University
Feinberg School of Medicine
Associated with Northwestern Memorial Hospital
Abbott Hall Suite 1004
710 N Lake Shore Drive
Chicago, Illinois 60611
Jason.ong@northwestern.edu

Indra Narang, MD
Title: Associate Chair, Faculty Development and Equity, Diversity and Inclusion, Department of Paediatrics
Designations: BMEDSCI, MBBCH, MD
Phone: 416-813-6346 ext. 309470
Email: indra.narang@sickkids.ca
Alternate Contact Name: Courtney Kennedy
Alternate Phone: 416-813-7654 ext. 414534
Alternate Email: courtney.kennedy@sickkids.ca
U of T Positions: Associate Professor, Department of Paediatrics
Other Positions: Director, Sleep Medicine, Division of Respiratory Medicine

Ariel B. Neikrug, PhD
Assistant Clinical Professor, Psychiatry & Human Behavior
School of Medicine
Phone: (714) 790-8406
Email: aneikrug@hs.uci.edu
University of California, Irvine
20350 SW Birch St.
Newport Beach, CA 92660