DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

March 14, 2018

The Honorable Adam Schiff
U.S. House of Representatives
2372 Rayburn House Office Building
Washington, D.C. 20515-0528

Dear Congressman Schiff:

Thank you for your letter to Dr. Michael Twery, Director of the National Center on Sleep Disorders Research (NCSDR) about sleep and narcolepsy research supported by the National Institutes of Health (NIH). The NCSDR is a component of the National Heart, Lung, and Blood Institute (NHLBI) at the NIH, and as the Director of the NHLBI, I am pleased to respond.

As you know, the NCSDR coordinates sleep research across the NIH and other government agencies. Thirteen NIH Institutes and Offices participate in the trans-NIH Sleep Research Coordinating Committee, and seven are currently supporting narcolepsy research.[1]

Over the past twenty years, we have made great strides in understanding narcolepsy. In 1998, NIH-funded research linked narcolepsy to abnormalities in the brain chemical orexin (hypocretin). This pivotal discovery capped a decade of intensive study into how sleep is regulated, and opened the door to wide-ranging research on the neurobiology of sleep that is underway today. Studies are investigating how the shortage of orexin interferes with the brain mechanism that sustains wakefulness and regulates sleep. We now know that the loss of orexin affects the regulation of rapid eye movement (REM) sleep, such that REM can occur whether the individual is asleep or awake. How the small cluster of orexin-containing neurons are damaged to cause narcolepsy is a focus of ongoing studies.

NIH-funded research is also discovering genetic and other risk factors that may contribute to the loss of orexin neurons. For example, a specific version of the gene called human leukocyte antigen (HLA), which is involved in the immune response, appears to increase the risk of developing narcolepsy by up to 25-fold. Studies are looking at whether people with this gene variant might be susceptible to forms of brain inflammation associated with severe infections that might then contribute to the loss of orexin neurons. These advances are enabling the systematic study of narcolepsy as a neurological disorder, the development of new diagnostic tools, and the customization of treatment strategies for better patient outcomes.

[1] The National Institute of Neurological Disorders and Stroke, the National Heart, Lung, and Blood Institute, National Institute on Mental Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institute of Nursing Research, the National Cancer Institute, and the Office of Behavioral and Social Sciences Research.

Novel pharmacotherapies for narcolepsy are also under development. To discover potential drug targets, NIH-funded researchers are examining the structure of the orexin brain receptor and how each part of the receptor interacts with other neuronal signaling mechanisms, and the types of brain signals that orexin neurons receive. Additional NIH-funded studies are investigating the chemical structure of the orexin receptor to identify molecules that could substitute for orexin. Pharmaceutical developers world-wide are leveraging this basic research to test novel drug candidates designed to reduce the severity of muscle paralysis that can be triggered by strong emotions in people with narcolepsy. Gene transfer experiments are also underway. These studies selectively add a special version of the orexin gene to key brain neurons. This work will determine whether the activation of these key neurons releases orexin and suppresses debilitating motor paralysis triggered by strong emotions in patients.

Scientific advances toward treatments for narcolepsy are stimulating a broad array of neuroscience discoveries with the potential to benefit all domains of sleep disorders research. For instance, orexin is only one component of the brain pathways stabilizing wakefulness. Ongoing NIH-funded studies in animal models, such as the fruit fly and zebrafish are enabling genetic and basic advances to understand not only how sleep is regulated, but also the role of wake-promoting brain signals from histamine and norepinephrine neurons. NIH-funded researchers have also discovered molecules that block orexin. This discovery has accelerated the development of a novel sleep-promoting drug (surovexant) by the pharmaceutical industry. Our growing understanding of narcolepsy and the role of orexin is being applied to better understand other conditions. For instance, because orexin deficiency appears to decrease opiate abuse in animal models, understanding the relationship between orexin and opiate brain pathways may lead to the discovery of new treatments to prevent opiate abuse. Ongoing studies also link orexin to brain pathways regulating appetite and insulin resistance in animal models. Further research is needed to realize the full potential of these discoveries and the health implications for narcolepsy.

Advances in narcolepsy and sleep research are increasingly dependent on the ability to directly measure the changes in body chemistry that quantify the larger potential health risks of narcolepsy and sleep deprivation. The Centers for Disease Control and Prevention estimate that in the United States (U.S.), 20% of adults and 70% of adolescents frequently obtain insufficient sleep. Whether caused by a sleep disorder, sleep deprivation, or irregular sleep schedules, the struggle to be awake has profound implications for public health and safety. A RAND study estimated that the economic burden of insufficient sleep in the U.S. alone exceeds $400 billion annually.[2] NIH-funded studies of sleep and sleep disorders indicate that human perception of sleepiness is not a reliable indicator of the need for sleep, nor of the impact of sleep deprivation on individual health or public safety.

[2] Why Sleep Matters-The Economic Costs of Insufficient Sleep: A Cross-Country Comparative Analysis. Hafner et al., Rand Health Q. 2017 Jan 1;6(4):11. eCollection 2017 Jan.

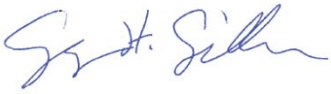
Identifying molecular signatures (biomarkers) that objectively indicate how the chemistry of the body is responding to sleep disorders and sleep deficiency will be critical for scientists to study the full range of related health risks. For instance, elevated levels of beta-amyloid (a biomarker of Alzheimer's disease risk) are linked to sleep deprivation. However, practical biomarkers to assess the biochemistry of sleep or circadian rhythms, or to help diagnose sleep disorders do not yet exist. While NIH has the analytical tools and expertise, specialized multi-disciplinary teams of researchers are needed to develop practical, medically validated products. Biomarker development has global implications. It would enable health care providers world-wide to diagnose disorders, such as narcolepsy, personalize treatment options, and assess the readiness of personnel involved in commercial transportation, military operations, and emergency response.

The above examples are just a few notable scientific advances in narcolepsy that highlight the critical role the NIH plays in supporting basic discovery research. These examples illustrate how fundamental knowledge is being translated and used by industry and the private sector to develop new therapies and other applications that extend well beyond narcolepsy. Advances in narcolepsy research play an important role to the vitality of the entire NIH sleep and circadian biology research portfolio.

As part of the NHLBI, the NCSDR is well-positioned to coordinate sleep, circadian, and sleep disorders research serving national imperatives in collaboration with trans-NIH and federal inter-agency working groups.

I hope this adequately addresses your questions, but if you would like additional information, such as a list of major publications or active NIH grants in narcolepsy research, please let us know. A copy of this response is being sent to all signatories on your letter.

Sincerely,



Gary H. Gibbons, M.D.
Director