The SCN lab is an integrated, multidisciplinary research facility dedicated to:

1. understanding sleep-wake control and biological rhythms at all levels from the molecular to the behavioral, and
2. developing new generations of pharmaceuticals to remedy the enormous unmet needs of sleep disorders medicine and disorders of circadian timekeeping.

The Stanford Sleep Disorders Clinic and Research Center (SSDSC) is directed by William C. Dement, M.D., Ph.D., the Lowell and Josephine Berry Professor of Psychiatry and Behavioral Sciences. Currently, the center is comprised of approximately 65 scientific, technical and administrative support staff. The facilities of the Center include over 3000 square feet of office space, 6000 square feet of research laboratories, and approximately 4000 square feet of animal housing/experimentation space. The SCN lab, directed by Seiji Nishino, M.D., Ph.D., is one of the major components of the SSDRC and is interactive with the Stanford Center for Narcolepsy (Director: Emmanuel Mignot, M.D., Ph.D.), the Stanford Center for Human Sleep Research (Director: Clete Kushida, M.D., Ph.D.), and other clinical research groups (led by Christian Guilleminault, M.D.) at the Stanford University Sleep Clinic (Director: Jed Black, M.D.).

The SCN lab has been built on the premise that:

1. Only an integrated, multidisciplinary approach will make rapid progress in understanding the neural, neurochemical and molecular mechanisms underlying biological rhythms and arousal state control, and
2. Understanding these mechanisms will lead to new opportunities and pathways for development of new types of pharmaceuticals for sleep disorders medicine and circadian rhythm disorders.

The research in this field is greatly facilitated by using proper animal models, and the SCN lab possesses various transgenic and gene targeting animals, including hypocretin/orexin gene knockout narcolepsy mice and hypocretin orexin cell targeting transgenic mice and rats, as well as other neuropeptide knockout mice.

The SCN lab benefits from being integrated within one of the finest research universities in the world; a university that fosters interdisciplinary ventures and applied research as natural outgrowths of scientific creativity. The origins of the SCN lab were in the Stanford Sleep Disorders Clinic and Research Center which has been the world leader in sleep research and sleep medicine for the past 35 years. The SCN lab itself was initially made possible by funding from industry. Which made it possible to assemble in one place an unprecedented amount of expertise in sleep and circadian rhythms research and to provide the finest and most advanced research equipment available. In turn, the scientists of the SCN lab designed and built the world’s largest and most technologically advanced facility for sleep and circadian rhythms research in animals.

At the heart of this facility is a state-of-the-art large scaled computerized sleep-wake and physiological monitoring system (64 animals simultaneously). All animals are housed in sound attenuated and light controlled individual closed chambers (see front page). One of our main sleep monitoring systems is the SleepSign program (Kissei America, Inc) now widely used by many sleep laboratories around the world. Before this software was introduced on the market, the Stanford Center for Narcolepsy evaluated and perfected the functions for the animal studies. The newer functions includes the MPEG video monitoring and recording system that can overlay on EEG signals, which is very useful in monitoring any behavioral changes during sleep recordings. This behavioral assessment is critical for pharmacological experiments testing new compounds. In addition, EEG and EMG, body temperature, drinking, and locomotor activity are monitored. Since all of these systems are capable of long-term monitoring, it allows us to monitor circadian rhythms for a large number of animals. Therefore, this core facility of the SCN lab has made possible, the ultimate level of research progress and drug screening/characterization.
SPECIAL RESOURCE AND MODEL SYSTEM FOR RESEARCH AND DRUG TESTING

- A large scale sleep-wake and circadian rhythm bioassay facility
- Automated data tracking and analysis computers to assure rapid, and accurate communication of experimental results to research sponsors
- Unique animal model systems include a narcoleptic rodent colony for testing alerting pharmacological agents and other genetically engineered mouse models.
- Pharmacology in sleep deprived animals
- Video monitoring and recording (MPEG) system synchronized with EEG signals
- In vivo microdialysis and HPLC analysis for neurotransmitter and regional drug delivery studies together with sleep monitoring
- Neurochemical assessments, such as radio receptor/gamma GTP bindings and radio enzyme-immuno assays and analysis of gene expressions (quantitative RT-PCR)
- Molecular biology laboratory

The SCN lab has continuous interactions with the Sleep Disorders Clinic and Research Center, which was the first clinical sleep center established in the USA and is widely recognized as the premier center in sleep medicine. This Center is led by Drs. William Dement and Christian Guilleminault. The Clinic has six fully-equipped sleep monitoring rooms for clinical services, five clinical research rooms, and access to the Clinical Research Center of the Stanford Medical Center. The continuous interaction between the SCN lab, clinical services and clinical research allows performance of well-integrated protocols and continuous feedback between clinical and fundamental research.

MAJOR RESEARCH DIRECTIONS OF THE CENTER

The current research foci of the SCN lab are concentrated in the following areas;

Hypocretin/orexin system and narcolepsy and other primary disorders of excessive daytime sleepiness (EDS)

From an extension on the findings in animals, it is now revealed that a large majority of cases of human narcolepsy is associated with a deficiency of the hypothalamic peptide, hypocretin/orexin. It is also shown that EDS associated with various neurological conditions, such as brain tumors, head injury and some immune mediated conditions (multiple sclerosis and acute disseminated encephalomyelitis) are often associated with hypocretin deficiency. Hypocretin replacement therapy is expected to have therapeutic effects in these conditions, although developments of small molecular non-peptide agonists are likely required. In our laboratory, we have a colony of hypocretin deficient narcoleptic mice and rats, and these animals sleep more (compared to their litter mate wild type animals) during active period and exhibit fragmented sleep/wake pattern and cataplexy-like behaviors (see below). These animals are ready for use in evaluating wake-promoting compounds and we will evaluate whether new classes of compounds improve/normalize abnormal sleep tendency in these animals. The therapeutic effects will be also characterized by comparison with wake-promoting compounds currently used, such as amphetamine-like compounds and modafinil.

Anticataplectic Medications

Anticataplectic medications, in addition to wake-promoting medication, is required for managing the symptoms of narcolepsy. Although cataplexy is often regarded as an abnormal manifestation of REM sleep atonia, our series of experiments suggests that there is a discrepancy between suppression of REM sleep and cataplexy. For example, dopaminergic D2/D3 antagonists reduce cataplexy, but do not reduce REM sleep. We are also using rodent narcolepsy models for evaluating anticataplectic effects, and in these models, evaluation of behavior cataplexy is subjective and not reliable. However, we believe that the effects on direct transition from wake to REM sleep (DREM) are more predictive for anticataplectic effects. DREM specifically occurred in narcoleptic animals during active periods and antidepressants strongly reduce and modafinil has no effect on
DREM; the effects mirrors the anticaataplectic effects of these compounds in humans.

Discovery Pathways to Treatment of Insomnia
We are also making major progress in elucidating the neural control of arousal state transitions and maintenance of arousal states. Studies of the mechanisms controlling REM and non-REM sleep homeostasis are bringing us closer to understanding the functions of these different stages of sleep. It is clear that insomnia and other disorders can have their roots in a variety of subsystems involved in sleep state control, for example, separate neurochemical agents that differentially affect REM sleep expression and REM sleep maintenance. Problems with either of these neurochemical systems could cause sleep fragmentation and insomnia (and EDS), but require different therapeutic approaches. Most of today's hypnotics are broad suppressants of neural transmission rather than agents that treat specific etiologies of sleep disorders. We believe that our research will lead to new generations of therapeutic hypnotics that will be tailored to specific sleep disorders.

Discovery Pathways to Wake Consolidation and Cognitive Enhancement
The research on the circadian control of sleep-wake has led to the discovery that a biological clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus interacts with a sleep homeostasis system by invoking an arousing stimulus at appropriate times in the daily cycle. Thus, the major regulatory constituents of the sleep-wake cycle are functional opponents—one promotes wakefulness and the other promotes sleep in response to the wakefulness imposed by the biological clock. Loss of the clock results in maximum sleep randomly distributed over the day. We believe that the discovery of the mechanisms by which the clock consolidates wakefulness will lead to the development of pharmaceuticals that will enhance alertness and help maintain wakefulness. One of the candidate systems that contribute to the clock dependent consolidation of wakefulness is the hypocretin system, since hypocretin release is highest at the end of active period and because the SCN lesion animal loses this diurnal fluctuation of hypocretin release. Populations that would benefit from these studies also include the elderly, shift workers, transporters and other workers in situations where alertness is vital. Such pharmaceuticals may also have a broad utility for ameliorating sleep-wake disturbances associated with jet-lag.

Discovery Pathways To Treatment Of Circadian Rhythm Disorders
The SCN, a small cluster of neurons just above the optic chiasm in the anterior hypothalamus, acts as a master clock, keeping time with an accuracy of a few minutes each day and adjusting body rhythms to seasonal variations in day length. The importance of this nucleus is apparent in people and animals with lesions of the SCN who may sleep and wake at any time of day.

The identification of genetic mutations in drosophila and mice have resulted in the description of a detailed intracellular translation-transcription feed-back loop (regulated by several transcription genes, such as Per 1-3 and Clock) that occurs in single SCN cells and generates highly accurate 24-hour rhythms to the rest of the organism. Mutations in the human Per 2 gene are shown to result in familial advanced sleep phase syndrome, one of the genetic circadian sleep disorders, and transgenic mice with this mutation are now available.

We have also begun to identify neurochemical inputs to the clock that phase advance and phase delays it, and we are refining our knowledge of the receptor subtypes that are involved. Several genes that are activated in the circadian clock in response to phase shifting stimuli have also been identified. We believe that this research program will lead to the development of phase shifting pharmaceuticals that can be used to allay the consequences of jet-lag and shift-work.

Experimental Drug Characterization and Evaluation
Drug development and drug screening can only be as efficient, sophisticated and accurate as the technology employed. We have repeatedly proven that our sleep evaluating system with various animal models makes it possible to fully characterize behavioral and physiological effects of drugs in record time and with a level of analysis and sensitivity that makes it possible to detect unanticipated effects early in the screening process. Finally, our bioassay system provides not only sleep-wake data but concomitant physiological and behavioral data essential for comparison with classical techniques in behavioral pharmacology. Thus, results from the SCN lab bioassays greatly enhance the quality of decisions about candidate pharmaceuticals.