

GROUPEMENT DE RECHERCHE SOMMEIL 2021/

SLEEP RESEARCH GROUP 2021

1. BACKGROUND AND RATIONALE OF THE SLEEP RESEARCH GROUP

A. SLEEP RESEARCH

I. General Scientific Background

In the 60s, French sleep research was widely acknowledged with the discovery of paradoxical sleep by Michel Jouvet and extensive work on narcolepsy by the team of Passouant and Billiard. Then, several French clinical research teams also contributed and improved the management of sleep breathing disorders (i.e. continuous airway pressure) and excessive daytime sleepiness (EDS) due to central hypersomnias. With more than a million patients under CPAP in France and more than 70 accredited sleep centers from the French Society for Sleep Research and Sleep Medical (SFRMS) and 700 centers prescribing OSA treatments sleep medicine has become a real medical speciality which has its own 1-year fellowship program (FST : formation spécialisée transversale) giving access to a medical degree in sleep medicine since 2018. To support this new specialty, active basic and clinical research are very important and the French teams have made major efforts to increase their productivity in the last years.

Animal models and exposure of healthy humans to sleep deprivation or intermittent hypoxia and clinical research in patients have increased our knowledge on the underlying mechanisms inducing the pathologies and contributed to the discovery of new therapies (mainly the wake-promoting compounds including modafinil and pitolisant) and the set up of new medical devices (dental appliances, neurostimulation to treat OSAS, digital CBT-I and neurofeedback to treat insomnia, light therapy, melatonin, wake therapy). E health is also a new burgeoning research field with in particular more than one million connected patients treated by CPAP downloading their data every night. Obstructive sleep apnea syndrome patients is the largest patient community followed in the world by connected devices, and numerous patients with insomnia using sleep app (>300 000 apps available in app stores worldwide) or connected devices (actigraphy, EEG headband, breath sleep inducer, relaxation devices, etc). More recently, sleep health is also acknowledged during development, and numerous studies have shown links between early-onset sleep disorders and developmental disorders such as autism or attention deficit hyperactivity disorder (ADHD) with their significant individual and societal burden, coming at high socio-economic costs to Western societies.

This should strongly drive innovation and valorization but it requires a strong clinical research infrastructure network specifically dedicated to sleep medicine. There is also a very strong need for collaboration between basic and clinical research with strong interdisciplinary projects (i.e. precision medicine projects). This is not an easy task since clinicians, basic sleep researchers and other scientists (i.e. AI, computer scientists, etc) may have different ways of thinking. The current project is to continue and expand the development of a network initiated in 2015 (first GDR 3737 sommeil) regrouping the different teams together to develop communication and collaboration between them.

In France, clinical research has been developed around sleep clinics operating in major Universities hospitals, frequently in connection with Clinical Investigation Centers from INSERM, accredited Reference centers based on the national orphan disease plan, and in some cities with Basic Research Units from INSERM and CNRS. The basic science teams are based inside universities and are generally members of neuroscience INSERM or CNRS laboratories. There are now links between the clinical research network and the basic teams working in sleep-

wake regulation, sleep physiology, circadian biology, chronotherapies, developmental aspects of sleep and animal models of sleep disorders (including rodent models of sleep apnea, narcolepsy, REM sleep parasomnia). Thanks to the first GDR these links helped us to significantly boost our scientific productivity in the last 5 years. These links need to be tightened to stimulate translational and interdisciplinary research.

The GDR has also a very tight connection with the French sleep research society (SFRMS). Benefits generated by SFRMS meetings, training and members fees have been reinvested in research and development, with grants offered for Master degrees, PhD, post doctoral positions, travels and biobanking in rare sleep disorders. It supports the neurophysiological bank of controls for normative data on sleep and vigilance (Normasom), a bank collecting all controls monitored during sleep for normative purpose and comparisons. The SFRMS has contributed in the past to support research by offering each year 2 to 3 full-time research assistant positions to help members of the SFRMS and the GDR to develop projects co-operated with INSERM, CNRS or ANR and involving major French sleep centers. Between 2015 and 2020, the SFRMS awarded 24 research grants on sleep and its disorders for a total amount of 475,000 Euros.

The Sleep Research network based on these SFRMS and GDR centers has a strong research structure based on identical neurophysiological and cardiorespiratory techniques including: polysomnography, multiple sleep latency tests, maintenance of wakefulness test, Osler tests, cardiorespiratory monitoring, nocturnal video analysis, vigilance tests. Centers have common scoring rules, and the ability to centralize scoring via exchange formats. These common capacities have been widely used in previous "Programmes Hospitaliers de Recherche Clinique" (PHRC, DGOS).

To increase interactions between sleep centers we created in 2015, the GDR sommeil (GDR 3737) which helped us to structure the community. Since then, major actions, recurrent meetings and projects helped us to increase very strongly the scientific productivity of the French sleep community.

Through the Rare Diseases Centers, organized in two reference centers and then one reference center (rare hypersomnias) since 2018 (PNMR3: Coordinator: Pr Y Dauvilliers, Montpellier) associated with competence centers spread out in the entire country, new techniques have been set up to better define the phenotype, the physiopathology and the biology of excessive daytime sleepiness (Biomarkers of sleep and wake states i.e. hypocretin/orexin, histamine/telemethylhistamine in CSF). A consensus for diagnosis and management has been performed and published to harmonize the procedures within sleep centers.

The constitution of a clinical and biological database has been made possible through the ANR grant "narcogene" and the PHRC grant "narcobank" and then narcoConx (2014), narcoT1 (ANR 2018) and narcomics (ANR ERA-NET 2018) which have given rise to several important publications (Lancet, Nature Genetic, Plos Genetic, Brain, Neurology, Sleep, Sleep medicine). Translational collaborations have been set up between basic research on animal models of primary hypersomnia and narcolepsy (and narcolepsy secondary to parkinsonism), as well as trials of H3-receptor inverse agonists in these models (Dr. Lin, CRNL, CNRS UMR 5292, INSERM U1028, UCBL Lyon 1, Université de Saint-Etienne) and then in patients.

In the field of OSAS and narcolepsy, several teams have set up systematic phenotyping using biomarkers of systemic inflammation and surrogate markers of cardio-metabolic risk: arterial stiffness, endothelial function, 24hour BP measurements, baroreflex, MSNA, etc. This strategy allowed the researchers to include outcomes in clinical trials that have not previously been properly assessed in sleep disorders. Pr. Pepin (INSERM U1300, UJF Grenoble), Pr. Gagnadoux (INSERM UMR 1063, Université d'Angers) and Pr. Roche (EA 4607, Université Jean Monnet Saint-Etienne) teams have an established clinical cohort representing the largest group of subjects with residual sleepiness in CPAP-treated patients. They are among the leading teams participating in the demonstration of the links between OSA and hypertension, diabetes cardiovascular disease and cancer. The Proof cohort is a reference cohort for the relationship between sleep apnea and autonomic alterations in elderly subjects (Chouchou et al, Eur Heart J, 2013). Moreover, these three teams are leading the national

registry of sleep apnea (> 70,000 patients prospectively for follow-up). The Pays de la Loire Sleep Cohort, a large multicenter clinic-based cohort including 12,000 patients investigated for suspected OSA between 2007 and 2017, is linked with the health administrative database (SNDS). The French Health Care database now covers 98.8% of the French population, over 66 million persons, from birth (or immigration) to death (or emigration). The linkage between clinical cohort's data and SNDS data makes the long-term follow-up easier with limited attrition bias contrary to trials.

In the field of Digital health several teams have developed innovative projects to implement numeric cohorts. The Grenoble team developed a software able to collect remotely questionnaires from the patients to enter them in a database. This software is now shared by more than 20 centers in order to collect clinical and paraclinical data. With the help of the EQUIPEX program PHENOVIRT, The SANPSY research unit (Bordeaux) developed virtual agents validated to perform clinical interviews to track sleep complaints, depression, addiction. During the COVID crisis these virtual agents have been implemented in free apps available in Google and Apple App stores to collect massive data (14000 downloads) on the general population and to deliver behavioral interventions to treat sleep complaints. The KANOPEE cohort developed with the data from the free apps allowed to produce a feasibility study showing that dCBT can be delivered through virtual agents and that these interventions improve significantly mild to moderate insomnia complaints (Philip et al, J Med Internet Res, 2020).

Emerging forces in the DGA research center (the CRESSA, French Army) are collaborating with sleep research teams and an associated clinical team joining the team of Pr. Leger and Dr. Chennaoui (VIFASOM, EA 7330, Paris Descartes Paris 5) has been accredited in the Sleep center of Hotel Dieu (Paris V).

In the field of circadian rhythms, very significant advancements have been made on the photic regulation of sleep, alertness and behavior. Thanks to transgenic mouse models (clock and/or photoreceptor invalidation), the Bourgin team (Lumière, rythmes, homéostasie du sommeil et neuropsychiatrie, UPR3212 CNRS, Strasbourg) demonstrated that the non-circadian direct effects of light are equally important to the circadian influence in shaping the 24-hr sleep-wake cycle; a finding that dramatically changes our understanding of the regulation of the 24-hr sleep-wake cycle. They uncovered that the SCN, beyond its clock function and contrary to previous beliefs, is a key mediator of the alerting effect of light. These findings allowed the set-up of a predictive model of the 24-hour sleep-wake cycle under alternative lighting exposure such as jetlags. In terms of novel concepts, they also showed that light can exert different and opposite effects depending on wavelengths composition (Bourgin and Hubbard, PLoS Biol, 2016; van der Meijden et al, Proc Biol Sci, 2018), pointing out the possibility of innovative therapeutics. In collaborative projects they developed innovative tools (pupillometer, E Van Someren, Amsterdam; electroretinography, M Hebert, Quebec) to define phototransduction-based indexes as diagnostic markers for sleep disorders (van der Meijden et al, Sleep, 2016). Finally, novel therapeutic applications include early morning light to counteract the negative impact of sleep deprivation (Comtet et al, Sci Rep, 2019) or light therapy (LT) as a first line treatment in seasonal and non-seasonal depression.

In the field of mental health, physician and scientific communities have an increasingly growing interest for sleep. This led to a better understanding of both manifestations, clinical course, sleep comorbidities, etiopathogenesis and response to treatments of mental disorders. This is also paving the way to a better personalized medicine in psychiatry, which is seriously lacking. In line with this quickly growing field, a French network for sleep and psychiatry (SoPsy) has been created 2 years ago, in the frame of the GDR and in collaboration with the SFRMS and the French Society for biological psychiatry (AFPB). This French network has already organized several meetings and published freely available documents including therapeutic recommendations (<https://www.afpbn.org/sections/sopsy/>). This network published numerous high-level publications and created a national database with common and standardized assessments regarding sleep and circadian rhythm biomarkers in depression (SoPsy-Depression, 36 psychiatric and sleep centers with close collaborations). Furthermore, a GDR working group focusing on sleep in neurodevelopmental disorders (NDD)

has linked the sleep community to NDD research networks in France (*GIS Autisme et Neurodéveloppement*) and in Europe, working among others on national and European birth cohorts including a total of 240 000 children and adolescents. These initiatives and achievements in the field of sleep and psychiatry with a life-span perspective have justified the creation of an independent research axis on “psychiatry” for the next funding period of the GDR sleep research group.

The SANPSY team has also contributed to develop research in sleep and psychiatry through partenarial publications on classification of sleep disorders and research in ontology applied to sleep and mental disorders (Gauld et al, Sleep Med Rev, 2021).

The structuration of the sleep community around major research centers developed with the help of the sleep GDR has allowed a significant increase in scientific production both in the field of basic and clinical sleep research and we are therefore strongly willing to pursue the adventure and renew the GDR (Sleep research Network).

II. Links between the clinical and pre-clinical research (translational approaches)

The clinical research group has strong links with basic teams working in sleep-wake regulation and the physiology and function of sleep. The historical basic teams are based in Lyon WAKING, and SLEEP team, CRNL, CNRS UMR 5292, INSERM U1028, UCBL Lyon 1, Université de Saint-Etienne). Both the SLEEP and the WAKING teams are members of the Labex CORTEX. In addition, a number of new teams in particular from Paris (e. g. Karim Benchenane, Gabrielle Girardeau) have joined the GDR, with a diversity of expertise. In the WAKING team, Dr. Gronfier is specifically involved in research in chronobiology and its interaction with alertness and cognition. His team collaborates with the SANPSY unit (Pr. Philip, CNRS UMR 3413, Université de Bordeaux) on an European space agency Grants as well as with the team of Pr. Leger (VIFASOM, EA 7330, Paris Descartes Paris 5), and that of Pr. Bourgin (CNRS UPR 3212). The translational team of Pr. Bourgin (CNRS UPR 3212) collaborates in the Chronobiotron (UMS 3415 CNRS-UdS) with Paul Franken (Lausanne), Luis De Lecea, Craig Heller and Emmanuel Mignot (Stanford University) in the field of chronobiology, alertness and mental disorders. WAKING team (Dr. Lin) has worked extensively in the regulation of alertness via the histamine system and development of animal models of narcolepsy and its treatment with H3-receptor inverse agonists (Pitolisant) and modafinil in partnership with Pr. Dauvilliers (INSERM U 106, Université de Montpellier 1) and Pr. Arnulf (CRCIM, INSERM UMR-S 975/CNRS UMR 7225, UPMC-Paris6) teams, as well as in the study of sleepiness in Parkinson models with Pr. Arnulf. This translational effort has allowed the French sleep group to be the first in the world to develop these drugs in humans. The SLEEP team, Pr Tafti (Center for Integrative Genomics, Switzerland), and Pr. Liblau (INSERM UMR 1043 / CNRS UMR 5282, Université Toulouse III) have collaborated with Pr. Dauvilliers team on an animal model of narcolepsy to study the physiology and physiopathology of REM sleep, the mechanisms of destruction of hypocretin neurons and related immune dysfunctions. Part of the preclinical research has involved BIOPROJET (Pharmaceutical industry) who have developed a new alerting anti-H3 drug (Pitolisant) and some other new drugs in this family. Other strong collaborations with Pharma were developed such as with JAZZ, Takeda, Idorsia, Theranexus (ANR narcoConx) to promote innovative wake-promoting agents. A similar translational project is highly operational on the control of muscle tone during sleep, with a REM sleep behavior model developed now in the SLEEP team in parallel with studies on RBD by three clinical teams (Pr. Arnulf team, Pr. Dauvilliers and Dr. Monaca teams). In the INSERM U 1300 (Laboratoire HP2, Pr. Pepin, UJF Grenoble), links between the cardiovascular consequences of intermittent hypoxia and sleep apnea are explored using animal models, exposure to healthy subjects to intermittent hypoxia (in collaboration with Harvard Medical school), translational and clinical research. Researchers are investigating general adaptations to hypoxia, not only during sleep but also during exercise and at high altitude. This is specifically the case regarding interactions between muscle, adipose tissue, brain and hypoxia.

Pr. Philip Team (SANPSY, CNRS USR 3413, Université de Bordeaux) is part of the LabEx BRAIN ("Laboratoire d'Excellence, Investissement d'Avenir", ANR) and has recently developed a partnership with basic research teams for the NUTRINEURO research unit (UMR INRA 1286 - Université de Bordeaux, Director S. Laye). The team plans to implement precision medicine programs in the field of sleep health combining virtual agents, dCBT and add on interventions and machine learning techniques to identify new patient's phenotypes and new personalized interventions. SANPSY also has a partnership through an ANR LabCom MEEGASAFE with the PHYSIP society to develop new methods to analyse wake EEG to develop solutions for the evaluating and management of sleepiness; with the PSA (Peugeot, Citroen) group through a LABCOM centered on human factors sleepiness, attention and autonomous driving. Finally SANPSY unit supports a co directed PhD thesis (Pr Philip) with the Labri Unit, INS2I CNRS (Dr Rouas) on vocal signals to predict fatigue and sleepiness.

Pr. Leger and Dr. Chennaoui (VIFASOM, EA 7330, Paris Descartes) teams collaborates on basic human research on cognition and sleep with Pr. Kouider and Thomas Andrilhon (Ecole Normale Supérieure, Laboratoire de Sciences cognitives et Psycholinguistiques CNRS/EHESS/DEC-ENS) and on basic research with Dr. Gallopin (Laboratoire Plasticité du cerveau, CNRS UMR 8249, ESPCI ParisTech).

Many studies have been implemented to develop innovative therapies in Major sleep disorders. For instance, obstructive sleep apnea syndrome (OSAS) is effectively treated by ventilatory support (Continuous Positive Airway Pressure, CPAP) or oral appliances. However, 15% of the patients initially refuse CPAP or discontinue to use it in the long term. Promising research is underway with electrical stimulation of the hypoglossal nerve or using vibratory stimulations (ANR TecSan Pasithea, Inspire clinical trial, IMTHERA trial).

Insomnia is also a major public health issue with several millions of patients and a large range of hypnotics. New sleeping drugs are being released on the market in targeted populations, including elderly people and patients with circadian rhythm disorders (i.e. shift workers, blind people, children with neurodevelopmental disorders including autism and ADHD, adolescents with delayed sleep phase syndrome ...). Some chronobiotic drugs (e.g. melatonergic agents) act on the circadian clock and have a new target compared to Benzodiazepines and Z drugs. Anti-orexin drugs also provide interesting approaches to treat insomnia. Developments of new, original D3 agonists in restless legs syndrome (which routinely affects 2% of the general population and is a major, neurological cause of insomnia) are ongoing in patients. Finally, non-pharmacological approaches (i.e. Cognitive Behavioral Treatment (CBT) have been validated as an effective treatment in sleep disorders and virtual tools (embodied conversational agents, virtual environments) are now tested to diagnose and treat sleep disorders.

In the last ten years, several other drugs have been developed to fight excessive daytime sleepiness, a disabling symptom found in many sleep disorders such as central hypersomnolence disorders (i.e. narcolepsy) but also in several medical conditions such as neurological, psychiatric and metabolic disorders. Development of new stimulants with an improved benefit-risk ratio is currently ongoing. French researchers were among the pioneers in this field initially with Modafinil (Lafon) and more recently with the promising Pitolisant and its family, Histaminergic H3 inverse agonist (Bioprojet). Other compounds such as modulators targeting cerebral proteins involved in intercellular communication, the connexins have the potential to increase drug efficiency (especially modafinil) and may represent a new promising approach (Duchene et al, Sleep 2016). More recently, new drugs, solriamfetol, non-sodium oxybate, sodium oxybate LP, and orexin receptor 2 agonists are promising innovative drugs to fight against sleepiness with strong relationship with Big pharma for their developments (Pr Y Dauvilliers, PI for most of these international trials)

Some devices have also been developed in the field of insomnia and chronobiological approaches with light therapy (through white, blue-enriched or red light) are a powerful tool to fight nocturnal sleep problems and disrupted circadian timing systems.

Major challenges still remain in the field of sleep physiology and pathophysiology of sleep disorders that justify the need for research networks such as the Sleep GDR to bring scientific centers together and conduct solid academic research to back up future translational research and discover innovative treatments.

III. European and international collaborations

Sleep deprivation studies have been strongly developed with European partners during the first GDR 3737 program. These studies involved France, Italy, Switzerland, Austria and England. These studies funded by the grant "Mission to Mars" examined the impact of confinement and chronic artificial lighting in men and women on sleep, mood and cognitive performances. In 2011, a study involving 2 French Chronobiology centers (Lyon, Bordeaux) was conducted in Concordia (a Franco-Italian Research Base located in the South Pole). This study developed countermeasures to insomnia in extreme environments, and found that specifically designed light spectra are effective in synchronizing the circadian clock and lengthening sleep in otherwise sleep-deprived individuals (Najjar et al, Plos One 2014). Such approaches have potential benefits for treatment of insomnia complaints in the general population and further studies have been conducted.

Several french teams (i.e.PA Geoffroy's, F Belvier, B Etain teams) also contributed with to International task forces on bipolar disorders and chronotherapeutics (Gottlieb et al, Bipolar Disord, 2019) and measuring circadian function in bipolar disorders (Murray et al, Bipolar disord, 2020).

Genetic approaches of rare forms of hypersomnias have been developed since the last 15 years at an European level with the European Network for Narcolepsy (EU-NN) created in 2008 by the European Sleep Research Society (ESRS)(Pr. Dauvilliers, member of the board at the beginning and then to the scientific committee, actual President: C Bassetti, Switzerland). In the field of sleep apnea, we have been able to design and conduct studies at the European level and have active collaborations with Switzerland, Spain, Belgium and Canada. Pr. Dauvilliers (INSERM INM, Université de Montpellier) and Pr. Arnulf (CRCIM, INSERM UMR-S 975/CNRS UMR 7225, UPMC-Paris6) teams have a partnership with Center for Integrative Genomics, University of Lausanne, Switzerland, and the Stanford Narcolepsy center USA for genetic studies on narcolepsy and Kleine Levin syndrome. Other strong collaborations were performed on pediatric narcolepsy and biomarkers with the Reference narcolepsy center in Bologna-Italy (Pr Plazzi).

The translational team of Pr. Bourgin together with Pr. Schroder (CNRS UPR 3212) has ongoing collaborations on circadian rhythms, non-visual effects of light and neuropsychiatric disorders with Paul Franken (Lausanne), Luis De Lecea, Craig Heller and Emmanuel Mignot (Stanford University), as well as with an international network focusing on the use of melatonergic drugs for children and adolescents with neurodevelopmental disorders.

Pr Philip and Pr Morin from the Laval University developed a partnership in the field of insomnia research. Pr Philip is associated professor in the Laval University and Pr Morin and Pr Bastien visited the SANpSY Unit during sabbatical leaves to develop research programs which contributed to collaborative publications. Pr Morin has been associated with the KANOPEE cohort project (Philip et al, JMIR, 2020) and will be involved in future publications on insomnia management through the KANOPEE cohort. In return professor Philip has co authored publications on the Canadian Insomnia Cohort managed by Charles Morin group. In the field of E health, Collaborations also exist with the Institute of creative technology (CAL, USA) (Pr Skip rizzo team) and articles have been published on virtual environments and cognitive remediation in the field of sleep and ADHD.

Pr. Dauvilliers and Pr. Leger teams have a partnership with Stanford epidemiological center for evaluation of sleep and sleep disorders in the general population of different countries. The SLEEP team has also collaborations on the neuronal networks responsible for inducing sleep with the two biggest asian laboratories, Pr. Huang (Shanghai, China) and Pr. Yanagisawa (Tsukuba, Japan), the leading sleep canadian laboratory, Pr. Peever (Toronto, Canada) and the leading Swiss laboratory, Pr. Adamantidis (Bern, Switzerland). Dr. Luppi is

also the President of the European Sleep Research Society and is therefore involved with Jean-Louis Pepin laboratory in the new European Grant on the diagnostic and treatment of sleep apnea, SLEEP revolution.

IV. Industrial partnerships

Partnerships have been created with BIOPROJET in the field of histamine agonists as well as dopamine agonists, JAZZ pharma and UCB pharma in the field of narcolepsy, idiopathic hypersomnia and restless legs syndrome. Other recent collaborations with Pharma were developed with Takeda, Idorsia and Theranexus (ANR narcoConx) to promote innovative wake-promoting agents such as orexin receptor agonist but also antiorexin drugs to treat insomnia. Accordingly, new “sleeping” drugs have also been developed or are in development to improve nighttime sleep in particular melatonergic agonists and anti-orexin.

Dental appliances and CPAP software and hardware validation to treat obstructive sleep apnea have also been developed with Resmed, Philips, Weinman and Air Liquide medical systems, plus recent start-ups. Design of virtual scenarios with Oktal, Immersion and Thales (Driving/ simulation and virtual situations as a virtual supermarket) to explore cognitive impairment in patients affected by daytime somnolence have been made possible via the PHENOVIRT program (Equipex Grant, Bordeaux). Physip company and the SANPSY unit manage ANR LAbcom in the field of EEG analysis to predict behavioral sleepiness.

Partnership with DEDALUS (the leading European information system company) on E health systems applied to the field of OSAS management are very active with the SANPSY team. The SANPSY unit is also a member of the PSA labCom (human factors) and a Phd Thesis is conducted on autonomous vehicles and human factors involved in take over.

In 2019 a spin off start-up from the SANPSY Unit named MY-MED-A was created to exploit a licence contract with the University of Bordeaux to commercialize Virtual agents in the field of sleep and mental disorders.

B. SLEEP MEDICINE

Sleep medicine is an innovative transversal medical field dealing with major public health issues. Epidemiological studies estimate that 5 to 20% of the general population suffers from insomnia and 5% of excessive daytime sleepiness. Obstructive sleep apnea (OSA) syndrome affects 8 % of the general population and this figure will increase with obesity epidemic and the aging processes. In the last 20 years, sleep medicine has been massively developed with more than 100 million euros of prescription of hypnotics (mainly by general practitioners) but also with more than 510 million euros/year for the treatment of obstructive sleep apnea by continuous airway pressure (550 000 patients on long term treatment). The sleep centers set up in public and private hospitals have allowed the implementation of clinical research centers working on cohorts of patients (i.e. rare diseases such as hypersomnia and narcolepsy or large registries for sleep breathing disorders).

Aside from patients, national and international epidemiological studies have shown the importance of sleep disorders and sleep deprivation as significant risk factors for traffic and industrial accidents. OSA, sleep quality and duration also massively impact the incidence and time course evolution of the pandemic obesity and type 2 diabetes. . Early onset sleep disturbances have been linked with highly prevalent neurodevelopmental disorders and worse developmental trajectories, increasing disease burden for young patients and families, and coming at a high socioeconomic cost. All these elements combined with profound changes in societal sleep habits (i.e. chronic sleep deprivation due to the 24/24 7/7 society) explain that sleep disorders and excessive daytime sleepiness are now a major public health issue.

The SFRMS has hugely evolved in parallel with the sleep medicine development, from a small society 20 years ago to now a society receiving 3000 attendants at the national yearly French sleep meeting. More than 70 clinical sleep centers have been accredited by the society on the French territory. A national sleep medicine

university diploma co-operated by the SFRMS and the Chest society trains 150 new MDs per year to become sleep medicine specialists.

Most recently, in 2018, a reform of the French medical studies by the higher ministry of education has introduced the creation of "formations spécialisées transversales" (FST) in sleep. This new training program based on European models will help training physicians to acquire a medical speciality in sleep medicine covering several organ specialities (pneumology, neurology, psychiatry, ENT, pediatrics, etc.). The creation of a medical specialty in sleep is a significant achievement and will pave the way for the dynamic extension not only of sleep medicine but also sleep research in France.

Beside members of the Sleep GDR participate in the organizing committees of International sleep and breathing conferences (Educational meetings jointly organized by European Respiratory society (ERS) and European Sleep Research society (ESRS) (2015, 2017, 2019), and the Alpine summer school in Lugano (2015, 2017, 2019). The Alpine summer school will be held in Grenoble in 2021.

2. FUTURE ORGANISATION OF THE SLEEP RESEARCH GROUP

A. OVERALL PRESENTATION

The sleep community share commons phenotyping tools (i.e. polysomnography) but many new methods have emerged with no standardization of the different techniques (biological markers in serum and CSF, genetic-epigenetic, imaging, metabolic, cardiovascular and cognition) in each research team of the network. Because EDS is a symptom with multiple phenotypes associated with many disorders (metabolic, cardiovascular, neurological and psychiatric), it is crucial to better phenotype patients and define new evaluation and normative data regarding healthy subjects and patients affected by excessive daytime sleepiness. While the polysomnographic definition of EDS is well known in patients (i.e. Multi Sleep Latency Test or Maintenance Wakefulness Test scores), its operational definition is still complex and multiple regarding healthy subjects in the ageing process and normative data are crucially lacking. The Sleep GDR will harmonize the phenotyping procedure which will be replicated in all the teams of the network. The development of new research platforms will be promoted with common clinical, neurophysiological and biological tools using the models from Bordeaux, Paris, Montpellier, Grenoble and Strasbourg. In several teams, a collaboration on the different cohorts will be implemented (i.e. KANOPEE in Bordeaux, 3 C in Montpellier, or Proof Cohort in Saint Etienne) to define normative values in healthy subjects across aging. International collaboration (i.e. European Narcolepsy Network) will be used to optimize the standardization of the procedure (on evaluation, diagnosis and management with EU guidelines for narcolepsy in revision 2021), to better understand the pathophysiology, and to develop new therapeutic drugs for patients with central hypersomnia that will help the group to obtain and conduct European grant.

The GDR will work on 5 main topics coordinated by 5 scientific leaders: central hypersomnias (narcolepsy, idiopathic hypersomnia, Kleine-Levin syndrome; coordinator: Pr. Dauvilliers), sleep apnea syndrome (Central and obstructive Sleep Apnea; coordinator: Pr. Gagnadoux) and behavioral somnolence/chronobiology (acute and chronic sleep deprivation, circadian, poor sleep hygiene disorders, insomnia; coordinator: Pr. Philip), neurodevelopmental and psychiatric disorders (sleep and sleep disorders in French and European pediatric populations (birth cohorts); sleep in mood disorders, suicidal behaviors, autism, ADHD, etc ; chronobiological treatments in sleep & psychiatry (light therapy, melatonin, wake therapies, CBT-I, IPSRT, wake drugs, etc)...; coordinator: Dr. Geoffroy), Basic research (Sleep/wake basic regulatory mechanisms, both neuronal and non-neuronal, developpement of research methods for EEG and beyond, etc. Dr Seugnet). Common translational

projects will be developed to improve understanding of physiopathology and the consequences of excessive daytime sleepiness (EDS) in order to help design new pharmaceutical and non-pharmaceutical treatments.

I. Central Hypersomnia

Sleep has been described as being of the brain, by the brain, and for the brain. This fundamental neurobiological behavior is controlled by homeostatic and circadian processes and is vital for normal brain function. Pr. Dauvilliers (INSERM INM - Coordinator of Team Neuropeps, Université de Montpellier) and Ohayon (Stanford Sleep Epidemiology Research Center (M.M.O.), School of Medicine, Stanford University) defined Operational Definitions and Algorithms for Excessive Sleepiness in the General Population with Implications for DSM-5 Nosology (Ohayon et al, Arch Gen Psychiatry 2012). Excessive quantity of sleep is widespread in the general population, co-occurring with a broad spectrum of cardiovascular, neurological and psychiatric disorders (Ohayon et al, Ann. Neurol. 2013). Excessive daytime sleepiness has recently been reported as a potential risk factor for mental health neurodegenerative and cardiovascular disorders, and death in elderly people (Empana et al, Stroke, 2009; Blachier et al, Ann. Neurol. 2012; Jausset et al, PloS One, 2013). Continuing this research program on sleep and ageing, future research will determine the potential underlying mechanisms involved in the relationship between daytime sleepiness and comorbid disorders.

Hypocretin /orexin deficiency results in the sleep disorder narcolepsy in many mammalian species, including humans, suggesting that the orexin system is particularly important for normal regulation of sleep/wakefulness states, and especially for maintenance of wakefulness (Dauvilliers et al, Lancet, 2007). Narcolepsy with cataplexy in particular is a disabling sleep disorder characterized by severe, irresistible daytime sleepiness (the most severe cause of hypersomnia) and sudden loss of muscle tone (cataplexy), caused by the early loss of neurons in the hypothalamus that produce hypocretin, a wakefulness-associated neurotransmitter present in cerebrospinal fluid (Dauvilliers et al, Lancet, 2007). The cause of neural loss in narcolepsy could be autoimmune since most patients have the HLA DQB1*0602 allele that predisposes individuals to the disorder. In close collaboration with the Genomic Research Center at the University of Lausanne, Switzerland (Pr. Mehdi Tafti) the Pr. Dauvilliers team reported an unexpected protective HLA DRB1*1301-DQB1*0603 haplotype (Hor et al, Nat. Genet., 2010). They also found that three loci located outside the HLA region were significantly associated with narcolepsy risk: T cell receptor alpha, Cathepsin H and Tumor necrosis factor superfamily member 4-TNFSF4 (Faraco et al, PLoS Genet, 2013). Elevated Tribbles homolog-2 specific antibody levels were found in narcolepsy providing evidence that this disorder may also be linked to a genetically determined underlying autoimmune disorder (Cvetkovic-Lopes et al, J. Clin. Invest, 2010). Narcolepsy is also associated with a higher frequency of vitamin D deficiency (Carlander et al, PLoS One, 2011).

In terms of public health risks, they also observed that H1N1 vaccination is strongly associated with an increased risk of narcolepsy-cataplexy in children and adults in France (Dauvilliers et al, Sleep, 2010; Dauvilliers et al, Brain, 2013). The mechanisms underlying its association remained unclear and further research is ongoing to elucidate its mechanism with close relationship with Drs. Peyron-Luppi team (équipe SLEEP, CRNL, CNRS UMR 5292, INSERM U1028, UCBL Lyon 1) and Pr. Liblau team (INSERM UMR 1043 / CNRS UMR 5282, Université Toulouse III) and Pasteur Institute (Dr. Walker), and Lausanne, Switzerland (Pr. Tafti). Work on immunological aspects of narcolepsy and related central hypersomnia are currently ongoing using animal models and the recent H1N1 vaccine model in human narcolepsy with objectives to define the mechanisms of neuroinflammation capable of inducing the death of hypocretin cells by injecting different combination of T lymphocytes. Early immune response will be dissected by histopathological studies and functional analysis of the CNS-infiltrating immune cells (Collaborations with Dr C Peyron-Luppi Lyon and Pr R Liblau Toulouse) with several key publications together (bernard-Valnet et al, Proc Natl Acad Sci U S A, 2016; Beltran et al, J Autoimmun, 2019, Nguyen et al, J Autoimmun, 2018; hartmann et al, J Exp Med, 2016). We also reported increased cytokine activities in patients with N1 (Lecendreux et al, J Autoimmun, 2015; Dauvilliers et al, Brain Behav Immun, 2014) and alteration in the microbiota (Lecomte et al, Neurol Neuroinflamm Neuroimmun,

2020). The large intravariability phenotype in narcolepsy may be driven by the role of each orexin receptor subtype, genetic background and the ageing process. We recently developed the first scale to assess the severity of narcolepsy symptoms and its modification with medication intake (Dauvilliers et al, Neurology, 2017; Dauvilliers et al, Sleep, 2020). The presence of both 'active' and 'negative' motor components of cataplexy has been highlighted in pediatric narcolepsy that favor a complex movement disorder at disease onset (Dauvilliers et al., BMC Med, 2013; Plazzi et al, Brain, 2011), together with a high frequency of depressive symptoms and altered health related quality of life in both adult (Dauvilliers et al, BMC Med, 2013; Dauvilliers et al, J Neurol Neurosurg Psychiatry, 2009) and children narcoleptic populations (Inocente et al, Sleep Med, 2014). Recent data showed that patients with narcolepsy have increased creative thinking (Lacaux et al, Brain, 2019). A cohort focusing on children affected with narcolepsy is currently following in the national reference centers for narcolepsy with specific tools created to assess prospectively the disease evolution and progression. We recently redefined the objective criteria and their cutoffs (MSLT latency) to diagnose children with narcolepsy (Pizza et al, Neurology, 2019).

Other orexin functions have been identified in regulating reward processing, emotion and mood, addiction, metabolism (Inocente et al, CNS Neurosci Ther, 2013) and autonomic system studied at the clinical level (Bayard and Dauvilliers, Front Behav Neurosci, 2013; Barateau et al, Neurology, 2020). A lack of perseverance and reduced performance on a decision making task, whether taking psychostimulants or not, was also reported, without any association with impulsivity, pathological gambling, or substance addiction (Barateau et al, Sleep, 2016). Patients with narcolepsy complained of attention deficit, with altered executive control of attention, with normal facial expression recognition and emotional regulation (Bayard et al, PLoS One, 2012; Bayard et al, J Sleep Res, 2013). A significant alteration in the autonomic nervous system was recently hypothesized in narcolepsy with a reduction in the amplitude of periodic leg movements-related heart rate responses (Dauvilliers et al, Sleep, 2010) together with a high frequency of the "non-dipping diastolic status" (Dauvilliers et al, PLoS One, 2012), which we also found to be associated with increasing risk of cardiovascular diseases and related stimulants intake (Bosco et al, Neurology, 2018). Potential links between central hypersomnia especially narcolepsy and attention deficit hyperactivity disorder were assessed in terms of biological and neurophysiological mechanisms but also in terms of benefit risk ratio of stimulants (Lecendreux et al, Sleep, 2015). Recent data showed that central hypersomnias are associated with a high frequency of depressive symptoms, depression and suicidal thoughts (Dauvilliers et al, J Neurol Neurosurg Psychiatry, 2009; Barateau et al, Neurology, 2020) suggesting that sleep alterations can impact mood per se. Ongoing studies in animal models suggest that narcolepsy-like disorders co-occur with depression-like behavioral alterations, thus supporting the idea that hypocretin plays key roles in functional connections between the control of sleep and of the psychoaffective tone. Identification of the underlying mechanisms notably the involvement of serotonergic and noradrenergic neurons is currently under investigation (Collaboration with Fabre V and Adrien J, UPMC Paris 6 UM 119, INSERM U 1130, CNRS UMR 8246).

Central hypersomnia also includes two more rare diseases, idiopathic hypersomnia and Kleine-Levin syndrome. Pr. Arnulf team (CRCIM, INSERM UMR-S 975/CNRS UMR 7225, UPMC-Paris 6) characterized the clinical phenotype of idiopathic hypersomnia in large cohorts (Vernet and Arnulf, Sleep, 2009; Vernet et al, J Sleep Res, 2010) and evaluated the benefit of new drugs in this disease (mazindol (Nittur et al, Sleep Medicine, 2013) and pitolisant (Leu-Semenescu et al, Sleep Med, 2014)). We recently developed the first scale that assesses the severity of idiopathic hypersomnia (Dauvilliers et al Neurology 2019). We also validated a well-standardized procedure to record the long sleep time in a bedrest condition to better diagnose patients with idiopathic hypersomnia (Evangelista et al, Ann Neurol, 2018). They also follow in France the world largest cohort of patients with Kleine-Levin syndrome ($n = 145$) (Arnulf et al, Brain, 2005; Arnulf et al, Ann of Neurology, 2008; Arnulf et al, Lancet Neurol., 2012; Lavault et al, Ann Neurol, 2015) with a research program focused on genetics (collaboration with Stanford university), functional brain imaging (Kas et al, Brain, 2014; Dauvilliers et al, PLoS One, 2014), as well as on long-term cognitive and psychiatric impairment, with innovative therapeutic research.

Recent data also support the use of lithium to prevent episodes (Leu-semescu et al, Neurology, 2015) and potentially IV steroids during symptomatic episodes (Leotard et al, Neurology, 2018). Eventually, they study central hypersomnias in the context of neurodegenerative diseases, mainly Parkinson's disease, with a research program on sleepiness and other sleep abnormalities in the presymptomatic phase of PD (idiopathic RBD, ICEBERG program in Investissements d'avenir ANR 10-IA-IHU 06), in genetic parkinsonism (LRRK2 mutations, Parkine mutation) and in patients with Parkinson's disease (Arnulf et al, Neurology, 2000; Arnulf et al, Neurology, 2002; De Cock et al, Nat Clin Pract Neurol, 2008; De Cock et al, Brain, 2011; Postuma et al, Neurology, 2012; Dauvilliers et al, Neurology, 2013; Garcia-Lorenzo et al, Brain, 2013), as well as in primate models of parkinsonism (collaboration with Chantal François, Etienne Hirsh, ICM; Belaid et al, J Neurosci, 2014) and in a cat model of parkinsonism (collaboration with JS Lin in INSERM, Lyon). In order to alleviate the severe sleepiness and motor deficiency of patients with PD, after a translational study of H3-receptor inverse agonists and dopamine agonists in an animal model of parkinsonism in Lyon, international drug trials on H3-receptor inverse agonists but also on modafinil and connexin inhibitors in PD have been conducted. In parallel, they studied the effects on alertness and sleep of deep brainstem stimulation (pedunculopontine nuclei) in patients in collaboration with Grenoble institute of Neurosciences (Arnulf et al, Ann Neurol, 2010) and later with the Pitié Salpêtrière ICM/INSERM.

Novel therapies targeting the orexin system and its projections on the histamine system for sleep disorders including insomnia and narcolepsy but also addiction and mood disorders remain particularly promising. Despite normal CSF histamine and tele-methylhistamine in hypocretin-1 deficient central hypersomnias and other central hypersomnias in older patients (Croyal et al, Ana. Biochem., 2011; Dauvilliers et al, Sleep, 2012) another recent CSF study revealed an impaired histamine transmission in narcoleptic children (Franco et al, CNSNT, 2019) and support the histamine therapy in narcolepsy. Indeed many studies in recent years reported the efficacy of a promising treatment (via a new class of wake-promoting compounds, i.e. H(3)-receptor inverse agonists, (Lin et al, Neurobiol Dis., 2008; Lin et al, J Pharmacol Exp Ther., 2011) which aims to reduce sleepiness and cataplexy in narcolepsy in adults (Dauvilliers et al, Lancet Neurol., 2013; Szakacs et al, Lancet neurol, 2017; Dauvilliers et al, Sleep, 2019) and in children (Inocente et al, Clin Neuropharmacol, 2012). Recent data also supported its use in treating residual sleepiness in the context of sleep apnea syndrome whether or not treated with CPAP machine (Pepin et al, Chest, 2020; Dauvilliers et al, Am J Crit Care Med, 2020). A very recent research project is dedicated to demonstrating the efficacy of a new potentiator of modafinil (a modulator, called THN02, targeting cerebral proteins involved in intercellular communication, connexins) in a controlled clinical trial and determining its mode of action but also to further understanding the involvement of connexin in wakefulness and sleep structures in close collaboration with the Theranexus Company, a spin-off of the French Atomic Energy Commission (CEA). The impact of THN02 on the arousing effects of modafinil in complementary animal models of narcolepsy and somnolence has been studied (Duchéne et al, Sleep, 2016), and this knowledge will be reinforced in future clinical studies, to characterize the mechanism of potentiation of modafinil by THN02, and then to demonstrate the efficacy of THN02 as a modulator of modafinil in patients with narcolepsy. Many other drugs, solriamfetol, non-sodium oxybate, sodium oxybate LP, and orexin receptor 2 agonists are under development and are promising innovative drugs to fight against sleepiness in patients with narcolepsy or idiopathic hypersomnia, but also Daridorexant (antiorexin for primary insomnia) with strong relationship with Big pharma for their developments and sleep centers in France (Pr Y Dauvilliers, PI for most of these international trials) (Thorpy et al, Ann Neurol, 2019; Bogan et al, Sleep, 2020; Dauvilliers et al, CNS drug, 2020; Dauvilliers et al, Ann neurol, 2020; Zammit et al, Neurology, 2020).

Finally, other research projects will determine whether the same network is recruited during REM sleep atonia and cataplexy. As cataplexy is quite rare in baseline condition, basic researchers (Dr. Luppi, Dr Peyron Lyon) are currently validating a protocol to behaviorally induce a sharp and very significant increase in cataplexy. They will determine whether there is an increased histaminergic neurons in the context of mice model of narcolepsy, and also whether the inactivation of the REM-generating glutamatergic neurons of the sublaterodorsal tegmental nucleus (SLD) suppresses cataplexy (Valencia Garcia et al, Nature Com, 2018). To this aim, they will

inject a Gi-DREADD transgene (with a cre-dependent expression) in the SLD of Hcrt knockout VGlut2-Cre narcoleptic mice. They will then inhibit the glutamatergic SLD transfected neurons with the designed drug clozapine-N- oxide (CNO) administered intraperitoneally a few minutes before the cataplexy induction phase. If the same network is involved in cataplexy and REM sleep, cataleptic episodes be abolished (Drs C Peyron-PH Luppi, Lyon).

To understand the cellular and molecular mechanisms causing central hypersomnia, it is necessary to identify potential new therapeutic targets. Thus, transcriptomic profiling in a mouse narcoleptic model is used to reveal genes and associated molecular signaling that are involved in the regulation of wakefulness, beyond known neurotransmitters. These genes are tested functionally using the flexible molecular genetics of Drosophila genetics and emphasize the role of metabolism in sleep-wake regulation (Farca et al, J Neuro, 2017; Aboudhiaf et al, Sleep, 2018, Drs Seugnet and Lin, Lab. Waking, CRNL, CRNL, CNRS UMR 5292, INSERM U1028, UCBL Lyon 1, Université de Saint-Etienne).

II. Sleep apnea syndrome

Animal models retain a central role in demonstrating the physiopathological mechanisms of sleep apnea syndrome. A feline model presenting all characteristics of OSA has been developed, i.e., periodic respiratory arrests during sleep, accompanied by an exaggerated respiratory effort and decreased oxygen saturation (Neuzeret et al, J Sleep Res., 2009; Neuzeret et al, Sleep, 2011). Because of the advantages of the cat for fine neurophysiological studies, the use of this model will further allow us to demonstrate the neural network controlling upper airways and musculature during sleep (Dr. Lin, Lab. Waking, CRNL, CRNL, CNRS UMR 5292, INSERM U1028, UCBL Lyon 1). In order to provide pharmacological treatments to OSA actually mostly treated by oral appliance, it is necessary to identify the neuronal network controlling the activity of the pharyngeal muscle during sleep. To this aim, our aim is to determine the neuronal network responsible for the muscle atonia of the pharyngeal muscle during PS. Ongoing experiments strongly suggest that the hypoglossal motoneurons (XII) involved in the control of pharyngeal muscles are inhibited during REM sleep specifically by GABA/glycinergic neurons located in a small nucleus located in the lateral medullary reticular formation, the lateral paragigantocellular nucleus (LPGi). Our project is to block GABA/glycinergic neurotransmission from LPGi neurons using transfection of VGAT shRNA in rats and to measure the tonus of pharyngeal muscle in addition to EEG and neck EMG. If the hypothesis suggesting that GABA/glycinergic LPGi neurons are responsible for the control of upper airway muscle tone during sleep is functionally confirmed, these neurons will constitute a new target for the pharmacological treatment of OSA (Luppi's Lab. Sleep, CRNL, CNRS UMR 5292, INSERM U1028, UCBL Lyon 1, Université de Saint-Etienne).

The hypoxic platform (U-1300) allows translational research into the pathophysiological consequences of hypoxia in various models and diseases. This platform uses cell models of endothelial, smooth muscle, cardiomyocytes, adipocytes and peripheral blood mononuclear cells exposed to sustained or intermittent hypoxia (IH) to study the biological mechanisms triggered at the molecular level by changes in oxygen availability. A rodent model has been developed as a tool (unique in Europe) to investigate the cardiometabolic consequences of sustained or intermittent hypoxia, mimicking the typical pathophysiological conditions of sleep apnea. This platform is available for the different teams of the group and has already been used by several teams: Pr. Gagnadoux team (UMR INSERM 1063, Université d'Angers), Dr. Monaca team (INSERM U1171, Université de Lille 2), Pr. Roche team (EA 4607, Université Jean Monnet Saint-Etienne), Dr. Luppi team (Lab. Sleep, CRNL, CNRS UMR 5292, INSERM U1028, UCBL Lyon 1, Université de Saint-Etienne). The platform can also be used for studies on healthy human volunteers exposed to either sustained or intermittent hypoxia, at rest, during exercise as well as during sleep (collaboration with Harvard University). This bench-to-bedside approach directly leads to clinical research into several pathologies involving systemic or local hypoxic stress such as chronic obstructive pulmonary diseases, sleep apnea syndrome, obesity, diabetes.

Translational research in OSA aims to demonstrate the specific activation of mechanistic pathways to determine new therapeutic targets.

4 examples:

- The leukotriene (LT) inflammatory pathway is activated in sleep apnea (OSA), obesity and diabetes (U-1300). In particular, strong evidence for the role of chronic intermittent hypoxia in the activation of the leukotriene pathway has been established by in vitro studies in isolated polymorphonuclear cells exposed to intermittent hypoxia, ex vivo studies performed in polymorphonuclear cells from OSA patients, mice exposed to chronic intermittent hypoxia, and clinical studies in OSA patients. The exposure of transgenic mouse models of obesity (*ob*-/-), dyslipidemia (*ApoE*-/-, *LDL R*-/-) or diabetes to chronic intermittent hypoxia will help us to understand the intricate association between intermittent hypoxia and multimorbid chronic cardiovascular diseases. The identification of eicosanoid profiles, in combination with a complete characterization of cardiovascular and metabolic phenotypes of patients, will help us to better understand the underlying mechanisms. This translational research will be of great interest for the definition of personalized therapeutic strategies for each patient, including new pharmacological or nutritional approaches. In this respect, interventional therapeutic trials with either 5-lipoxygenase inhibitors or five lipoxygenase activating protein inhibitors or with n-3 polyunsaturated fatty acid supplementation will be performed both in experimental mouse models and in humans.
- The nonmuscle myosin light chain kinase (nmMLCK) isoform is a protein that contributes to endothelial cell-cell junction opening and monocyte migration, and therefore participates in inflammation (ANR nmMLCK 2012-14 Angers-Grenoble). By combining basic research in animal models, molecular studies in different types of cell culture and biological and genetic analyses in humans, we aim to: (i) validate the molecular implication of nmMLCK in intermittent hypoxia-associated inflammation and vascular effects, (ii) evaluate nmMLCK as a biological marker of the severity of OSA, and (iii) analyze the association between nmMLCK polymorphisms and OSA.
- Circulating microparticles (MPs) are small plasma membrane vesicles that can be released by a variety of vascular or blood cells, and contain both membrane and cytosolic elements. A growing number of studies have recently focused on the role of MPs in the atherogenic process. INSERM unit 1062 (R Andriantsitohaina, MC Martinez) has developed an original research on the role of MPs in OSA-associated cardiovascular dysfunction. Clinical studies have shown that levels of MPs of various cellular origins, including platelets, endothelial cells and leukocytes, are increased in OSA patients. Circulating levels of MPs harbouring markers of cellular activation or apoptosis that are known to predict poor cardiovascular outcomes were found to be correlated with OSA severity as well as markers of vascular impairment, and were modified by OSA treatment. As potential biomarkers of vascular dysfunction, MPs could provide a useful tool to predict cardiovascular outcome and monitor treatment response in OSA patients. Experimental data suggest that MPs may contribute to the pathophysiology of OSA-associated vascular impairment by promoting endothelial dysfunction, inflammation and vascular hyperreactivity. Thus, MPs may emerge as a novel biological vector of vascular dysfunction adding another layer of complexity to the already multifaceted mechanisms involved in OSA-associated vascular morbidity. Further studies are required to investigate the pathways through which MPs may impair vascular function in OSA and to determine whether MPs could constitute a novel therapeutic target to improve cardiovascular outcome in OSA. The contribution of circulating exosomes and the miRNA they carry to the development of endothelial dysfunction in patients with OSA is currently evaluated.
- The interconnections between hypoxia and circadian rhythms have become a particularly crucial research topic in physiology. This interaction is largely related to epigenetic mechanisms and

chromatin dynamics. There is little or no data on these interactions in OSA, a disease of particular interest for this theme since intermittent hypoxia occurs only during a specific circadian period (sleep). This is therefore an important emerging area to explore and the main objective of this project is to demonstrate that the reprogramming of circadian homeostasis by chronic intermittent hypoxia is a key mechanism in the development of organ damage related to OSA, with a particular focus on liver disease. Given the intimate link between hypoxia, circadian rhythms and chromatin dynamics, understanding how these components interact will allow the TEMPORISE project to shed light on the contribution of these factors in the progression of liver damage during OSA. First, we aim to explore the kinetics of the evolution of liver damage during exposure to intermittent hypoxia and to characterize the timing of the disruption of circadian rhythms due to intermittent hypoxia. Next, we wish to understand the molecular mechanisms involved in this deregulation by studying the interactions between the circadian clock and HIF-1 and their involvement in the regulation of gene expression. Finally, we will analyze the effects of the disruption of the circadian clock and HIF-1 on the development of ICH-induced liver damage using appropriate knock-out mouse models. The combined expertise of the coordinator and partners is a major asset for the TEMPORISE project. This project will use cutting-edge techniques such as epigenomics, transcriptomics, proteomics and bioinformatics approaches. At the end of the project, we hope that the discovery of new molecular mechanisms will provide important information for the understanding of the development of liver diseases and will open new perspectives for pharmacological interventions.

Clinic- and population-based cohort studies aim to evaluated OSA-related health outcomes and the impact of OSA treatments:

OSA is increasingly recognized as a risk factor of cardiovascular diseases (CVD) and metabolic dysfunction. However, the cardiovascular and metabolic benefits of OSA treatment with continuous positive airway pressure (CPAP) remain uncertain, with recent randomized clinical trials failing to demonstrate a reduction in CVD events or mortality. A potential source of these discrepant findings is the substantial heterogeneity of cardiovascular risk across different phenotypes of OSA. This heterogeneity may be partly related to differences in the acute physiological consequences of the upper airway obstructions during sleep. There is a growing consensus that common polysomnographic indices, including AHI, arousal index, and oxygen desaturation index, does not adequately capture the acute physiological or long-term health consequences associated with this OSA. To address this problem, several research programs aim to identify novel measures that may more accurately quantify respiratory event-specific hypoxemia, arousal intensity, and autonomic response. Recent study performed within the Pays de la Loire Clinic-based cohort, have demonstrated that polysomnography- or single channel oximetry-derived indices of hypoxic burden, heart rate or pulse variability, may provide an opportunity to allow for stroke or atrial fibrillation risk stratification in patients with OSA (Blanchard et al, ERJ, 2020; Blanchard et al, Ann Am Thor Soc, 2021).

Epidemiological studies have shown that sleep apnea is associated with increased risk of several types of cancer and can lead to poorer treatment outcomes. Biological mechanisms underlying the link between chronic diseases and cancer are complex and still not fully understood. Sleep apnea is associated with low-grade inflammation activating the NF- κ B pathway, a common characteristic of many tumors and which is associated with insulin resistance. Malignant cells are able to survive hypoxia through the activation of a family of Hypoxia-Inducible transcription Factors or "HIFs" which behave as oncogenes and are responsible for tumor angiogenesis, proliferation, invasion, metastasis and resistance to radiation and chemotherapy. Similarly, HIF activation can impact proliferation and differentiation of leukemic stem cells via transcriptional regulation of genes like FOXO. Some oncogenic pathways playing a major role in leukemic proliferation, like PI3-AKT pathway or mTOR (leukemia) are also regulated by levels of HIF. There is thus growing evidence that hypoxia is among the major events undergone by malignant cells during tumor progression. This link between sleep apnea and cancer is a hot topic and several studies from Angers and Grenoble teams are ongoing. A recent study from the

Pays de la Loire Sleep Cohort has demonstrated that global nocturnal hypoxemia mediates the relationship between OSA and cancer, particularly lung cancer (Justeau et al, Chest, 2020). The impact of CPAP therapy of OSA on cancer incidence is currently evaluated. The multicenter NEOSAS cohort (collaboration Angers University-French Research Network on Thoracic Cancer, GFPC-IMRB Crêteil) has included 1,200 patients with newly diagnosed lung cancer and will evaluate the impact of OSA on progression free survival. Artificial intelligence offers a promising opportunity to develop algorithms integrating clinical data, comorbidities and new polysomnographic indices for phenotyping and risk stratification in OSA patients. The *Predivasc* project, in collaboration with the Ecole Supérieure d'Electronique de l'Ouest (ESEO) and the CIDELEC company, aims to develop cardiovascular risk stratification algorithms using AI within the Pays de la Loire Sleep Cohort.

The PROOF cohort (UJM St Etienne) is cited in almost all meta-analyses evaluating the different cognitive, cardiovascular consequences of sleep apnea in elderly subjects. In 2019 the number of endpoints (mortality and CV disease) sufficient to meet the primary and secondary objectives of the Proof study was achieved: the independent role of autonomic impairment as a marker of cerebrovascular and cardiovascular risk and the impact of OSA after 65 yrs. The longitudinal follow-up of this cohort makes it a "model" cohort for aging well and will also be the subject of collaborative studies to test the validity of new blood or paraclinical biomarkers of biostress (D Gozal Research Team, MO, USA; C Mariat, Inserm CIRI team University of Lyon). The Voilage study (Grant 2015 CHU still in progress) evaluates the particular vulnerability of young apneic patients to intermittent hypoxic stress (in comparison to the elderly subject). A new study will test the changes in total water content in the hippocampus and cortex in the apneic subject and its reversibility under night-time CPAP treatment (Grant 2018 CHU in progress). The role of ambulatory blood pressure and hypertension on gray matter loss in elderly subjects but also on vascular fragility at the level of white matter is also evaluated in collaboration with the Cardiology and Hypertension Department of Bordeaux University Hospital (Philippe Gosse).

The diagnosis of sleep apnea is costly and long waiting lists delay the treatment of patients. It would be useful to have a screening test also linked to disease severity. As sleep apnea is associated with inflammatory and oxidative stress, we propose to use the detection of patterns of disease-related volatile organic compounds (VOCs) in exhaled breath using sensor arrays on the basis of cross-reactive gold-nanoparticles coated with organic ligands. Indeed, this approach may offer several advantages, including: easy-to-perform, direct and real-time monitoring of SAS. These devices have been tested for early detection of cancers and other diseases states as Primary Pulmonary Hypertension showing an ability to distinguish not only between different types of disease, but also between early and advanced stages of the disease (Cohen-Kaminsky et al, Am J Respir Crit Care Med, 2013). The feasibility of an array of cross-reactive molecularly-modified gold-nanoparticle sensors, in conjugation with pattern recognition methods, will be explored for detecting and classifying SAS. This work will be done in collaboration with the International Associated Laboratory INSERM-TECHNION of the DHU Thorax Innovation (Service de Pneumologie, Hôpital Bicêtre, Le Kremlin-Bicêtre).

The linkage of clinical cohorts with health administrative data provides the opportunity to evaluate the impact of sleep-related breathing disorders on health expenditures. A medico-economic research program is currently developed with a collaboration between the Pays de la Loire Sleep Cohort and the CESP, INSERM UMR 1018 (Dr Nathalie Fleury).

Finally, in an attempt to improve treatment adherence and patient's support several studies have been performed using telemedicine. These suggested that according to patient's clinical presentation not all patients would benefit from support from telemedicine. Actually, the patients with highest cardiovascular risk may benefit while patients with low would not (Pepin et al, Chest, 2019 ; Tamisier et al, Chest, 2020). Virtual agents have been used in ecological environments and demonstrated their ability to be used by home care technicians and patients to quantify excessive daytime sleepiness (Dupuy et al, J Sleep Res, 2020). Personalized interventions designed to treat insomnia (Philip et al, JMIR, 2020) have shown promising results and be applied to OSAS patients to improve sleep quality. Further research on telemonitoring from CPAP devices is now

engaged to link patients trajectories to clinical phenotype of patients. This should allow personalization of treatments that are dedicated to different groups of patients.

III. Behavioral somnolence and chronobiology

Sleep hygiene and sleep health are growing concerns in modern societies, which face chronic sleep deprivation. The modulations of neurobehavioral functions (e.g., alertness, psychomotor vigilance executive functions, short-term memory) are known to depend on the circadian system, the homeostatic process (sleep pressure) and on systems promoting alertness (waking systems). The homeostatic process, which increases exponentially with duration of prior wakefulness and decreases during sleep, interacts with a circadian process driven by the biological clock to regulate the sleep–wake cycle. The systems promote alertness (orexin/hypocretin, histamine, norepinephrine and epinephrine) and regulate the level of arousal. An increase in homeostatic pressure by extending wakefulness is a key strategy to treat insomniacs by a cognitive behavioral approach. Histamine and orexin neurons play distinct, but complementary and synergistic roles in the maintenance of wakefulness. Animals' deficient of histaminergic neurotransmission show permanent somnolence associated with EEG and behavioral deficits (Anaclet et al, J Neurosci, 2009; Lin et al, J Pharmacol Exp Ther., 2011; Parmentier et al, J Neurosci., 2002). Histamine is supposed to set cortical dynamic favorable to cognitive functions. Indeed, normalization enhancement of histamine transmission using H3 receptor inverse agonists (Pitolisant, e.g.) produces clear anti-somnolent effects and improves cognitive outputs in behavioral somnolence associated with diverse causes in animals and humans. (Gondard et al, Neuropsychopharmacology, 2013; Inocente et al, Clin Neuropharmacol, 2012; Parmentier et al, Neuropharmacology 2016). Patients with low hypocretin-1 concentration (i.e. narcoleptics) have shorter sleep latency during the Multiple Sleep Latency Test than patients with normal hypocretin-1 concentration. One important issue is to identify the epidemiology of sleep loss and to differentiate voluntary and involuntary short sleepers, due to several factors: work, social jetlag, transportation time, internet and new technologies, but also insomnia or disturbed environmental conditions. Too short sleep concerns about one third of young adults, professionals, but also adolescents and insomnia with daytime consequences 19% (Leger et al, Sleep Med., 2011; Leger et al, PLoS One, 2012). More standardized methods have to be developed to assess objectively the magnitude of sleep loss by actigraphy or simplified polysomnography and its biological consequences. A chronic semi-ecological sleep restriction leads to a depletion of stress system (cortisol and alpha-amylase) and testosterone during the daytime period together with lower cognitive performance (executive inhibition function and memory task) while short repeated blue light exposures improve all these parameters tested (Faraut et al, Front Neurosci., 2020). An alternative countermeasure to sleep debt, banking chronically sleep before a total sleep deprivation, show limited beneficial effects on cognitive decline (working memory and executive inhibition function) following sleep deprivation (Rabat et al, Front Neurosci., 2019).

In the field of chronobiology, Gronfier's group showed that circadian rhythms disappear during coma, that their restoration is associated with improved cognition and consciousness, and suggested that circadian rhythmicity may be a prerequisite for coma recovery. This group also demonstrated that light induces cerebral and extracerebral responses (pupillary reflex, skin temperature, EEG, ECG) within 1-5 minutes of light exposure at modest illumination levels (Prayag et al, Frontiers Neurosci, 2019), and that melatonin secretion can be inhibited at extremely low light intensities, below those observed in urban areas at night and from LED screens (smartphones, computer and TV screens, Prayag et al, J Pineal Res, 2019.). This work under highly controlled (constant routine) conditions has shown that light sensitivity fluctuates over the 24 hours, and that the biological clock drives this response by controlling both pupil diameter (Daguet et al, Frontiers Neurol, 2019) and photoreceptors' sensitivity (rods, cones, and melanopsin, Daguet et al, under revision 2021). Work in collaboration with Harvard Medical School revealed that the inhibitory effect of light on melatonin secretion (inhibitor) is very rapid, does not dampens during the night, and that melatonin suppression cannot be used as a proxy for circadian sensitivity to light (Rahman et al, J Physiol, 2019).

While sleep restriction theoretically decreases neurobehavioral performance and induce somnolence, not all individuals are equal with regard to sensitivity to sleep loss (Galliaud et al, J Sleep Res, 2008; Leproult et al, Am J Physiol Regul Integr Com Physiol, 2003; Philip et al, J Sleep Res, 2004; Rupp et al, Sleep, 2012; Van Dongen et

al, Sleep, 2004). Some individuals are resilient to sleep deprivation while others are more vulnerable. Regarding the genetic variation of adenosine receptor, haplotype analyzes confirm the influence of several single nucleotide polymorphisms of ADORA2A on total sleep time (Erblang et al, Genes, 2019).

These findings are promising to better understand vulnerability to sleep loss in healthy subjects and patients, they could also help to design customized drugs or countermeasures for healthy subjects (i.e. military) or patients who suffer from daytime sleepiness. Finally they would also help in the design of new treatments for insomniacs. Subjects with high levels of orexin will be very good responders to almorexant type drugs when other could benefit from cognitive behavioral treatments (i.e. sleep restriction and stimulus control). Indeed one of the key issues is that many insomniacs no longer respond to hypnotics after a few weeks of treatment (Morin et al, JAMA, 1999). A customized approach based on a better phenotype of insomniacs could help in selecting the optimal responders to hypnotic treatment. According to our preliminary results on rats, humans who sustain their performances under sleep deprivation (or extended wakefulness) could be good candidates for anti-orexin drugs. A combination of antiorexin drug and sleep restriction could be very beneficial in these subjects. Other new “sleeping” drugs may be promising for our field and are currently in development with solid collaborations with sleep centers of the GDR network, such as melatonergic agonists (i.e. tazimelteon in blinded subjects, Collaboration with Vanda, Pr. Leger), and oxycodone/naloxone to manage a severe cause of insomnia i.e. restless legs syndrome (Mundipharma, Collaboration with Pr. Dauvilliers).

One field of research to be developed is the cognitive and objective assessment of sleepiness to evaluate accidental risk of patients. Bioulac (Bioulac et al, sleep, 2017) published a meta analysis study showing that self perceived sleepiness at the wheel is a strong predictor of driving accidents. In line with this work another study (Philip et al, Scientific Reports, 2020) on 70000 OSAS patients showed that self perceived sleepiness is a better predictor of driving impairment than AHI.

The Maintenance Wakefulness Test (MWT) is a test widely used in clinics to determine the ability to stay awake in a soporific situation. It is also used in a forensic setting. Although the MWT is increasingly being used, there was no clearly established normal value making its probabilistic value regarding driving accidents weak, Several recent studies showed the relationship between objective measures of sleepiness and driving impairment (Sagaspe et al, Sleep Med, 2019) and more recently driving risk reported by patients (Philip et al, Sleep Med, 2020). A new sleep latency analysis based on microsleep analysis will provide a better correlation with cognitive performance (led by L. Peter-Derex and M. Strauss) and a better predictor of accidental risk.

Poor sleep hygiene impact insomnia complaints and cognitive and behavioral therapies are efficient in the treatment of insomnia but very time consuming for the sleep specialists. The Bordeaux sleep clinic (Pr. Philip, GENPPHAASS team, SANPSY, CNRS USR 3413, Université de Bordeaux) in partnership with Montpellier Paris and Lille sleep centers has obtained a PHRC-N (PROPERSON 2014) to develop internet-based programs to help insomniac to withdraw hypnotic therapies and replace it by CBT treatments.

In the current days with as much as 60% of the general population reporting sleep complaints there is a huge need to track and treat mild forms of insomnias to reduce the consequences of social stress.

We have since the beginning of the 2020 confinement developed virtual agents available on Google store and Apple store (KANOPEE project) which has demonstrated their ability to track and treat mild to moderate insomnia complaints (Philip, JMIR 2020). In addition, the KANOPEE project made it possible to collect on 2455 subjects sleep logs during 7 consecutive nights showing that filling up an electronic sleep agenda can significantly improve sleep complaints. Defining specific phenotypes of these subjects able to improve their sleep by monitoring it, is a new axis to explore to personalize sleep hygiene campaigns.

Indeed, A relevant scientific challenge is the identification of the determinants of adherence and response to digital interventions and cognitive behavioral therapies. Analysing responders and non-responders to these dCBT is a major aim for the new years of research in order to define treatment trajectories. Psychological but also biological markers could be involved in these response profiles. We showed that the use of virtual agents

(Philip, N Digital medine 2020) optimize trust and empathy for the human machine interactions but other determinants probably play an active role in adherence to digital behavioral treatments.

IV. Neurodevelopmental and psychiatric disorders

Psychiatric disorders are very common, affecting one quarter of the general population (Charlson et al, Lancet, 2019), and are the leading cause of years lived with disability (YLD) worldwide overall (Whiteford et al, Lancet, 2013) and of disease burden in children and adolescents (disability-adjusted life years, DALYs, in 5-14 year-olds, WHO 2016) . Surpassing both cardiovascular disease and cancer, psychiatric disorders constitute 13% of the global burden of disease (Collins et al, Nature, 2011). Addictive disorders are also a major public health problem, with a steady increase in their prevalence (+100% in 10 years) (Global Burden of Diseases, Lancet, 2018). Suicide attempts are the second leading cause of morbidity in Western countries, particularly among adolescents/young adults and the elderly (Fazel & Runeson, NEJM, 2020). An effort by the international medical and scientific community has led in recent decades to a better knowledge of vulnerability factors, in particular genetic determinants, environmental factors and biological pathways involved in mental disorders and addictions. Unfortunately, to date, the accumulation of knowledge has not been accompanied by a significant better understanding of individual trajectories, prevention strategies, nor by a significant improvement in our therapeutic strategies.

In recent decades, sleep abnormalities have emerged as promising clinical biomarkers for psychiatric disorders, contributing to the pathogenesis, symptoms and risk for relapse of these disorders. Indeed, sleep disturbances are core symptoms of substance use disorders and psychiatric disorders (Geoffroy et al, Biological Psychiatry, 2018; Dolsen and Harvey, Addiction, 2017). For example, more than 90% of individuals with major depressive episode have an insomnia or hypersomnia complaint (Geoffroy et al, J Affect Disord, 2018). Sleep and circadian alterations are also worsening psychiatric symptoms and resistance to psychotropics (Schröder CM, O'Hara R, Ann Gen Psychiatry, 2005; Lopez et al, Sleep. 2019; Yavuz-Kodat et al, J Clin Med, 2020). Sleep alterations appear to be one among the best predictors of suicide attempt among adolescents (Mars et al, Lancet Psychiatry, 2019) and among individuals misusing alcohol (Chakravorty et al, Addict behav, 2014). Sleep alterations have been also demonstrated by one of the GDR team to predict suicidal behaviors, independently of all psychopathologies and known risk factors (Geoffroy et al, Mol Psychiatry, 2020). Sleep alterations are furthermore a well-known risk factor of relapse into substance use (Garcia and Salloum, Am J Addict, 2015; Putnins et al, J Clin Psy, 2012; Sylvia et al, J Psychopharmacol, 2012). In this context, prevention and treatment of sleep disturbances might be an efficient strategy to decrease the risk of onset or relapse of psychiatric disorders.

Regarding mood disorders, more specifically, we contributed to demonstrate that alterations in sleep and biological rhythms are a central phenomenon of mood disorders (Geoffroy , Biological Psychiatry, 2018). These are "trait" markers, i.e. they are present even during remission phases, such as poorer sleep quality and efficiency, higher variability of sleep-wake rhythms, increased REM sleep and shorter REM sleep latency (Geoffroy et al, J Affective Disorders, 2014; Geoffroy et al, Acta Scand Psychiatrica, 2015; Bertrand et al, J Affective Disorders, 2021). They predict thymic recurrences and complications, including suicidal behaviour (Wirz-Justice and Benedetti , Eur J Neurosci, 2019; Geoffroy et al, Mol Psychiatry, 2020). We have highlighted a genetic vulnerability regarding several core clock genes (*RORA*, *TIMELESS*, *NPAS2*, and *ASMT*), and we were also able to better characterize sleep phenotypes in these patients (Etain et al, Chronobiol Int, 2014; Geoffroy et al, Genes Brain and Behavior, 2014; Geoffroy et al, Scientific Reports, 2015). We contributed too to delineate alterations of the phototransduction pathway in mood disorders, including alterations of the melanopsin pupillary reactivity (Stephenson et al, Sleep Med Rev, 2012, Rach et al, J Sleep Res, submitted). Some polymorphisms of these core clock genes on PGC1A and RORA have been also associated with lithium

response, the cornerstone treatment of bipolar disorder (Geoffroy et al, Genes Brain and Behavior, 2016). Transcriptomic studies have shown interesting differences of core clock genes expressions associated with lithium response (Geoffroy et al, World J Biol Psychiatry, 2018).

Neurodevelopmental disorders (NDD) also benefited from this increasing interest regarding sleep biomarkers. Several structuring projects have been initiated across France and Europe, with effective collaborations between our sleep GDR subgroup on NDD (lead by Pr. C Schroder and Scientific Interest Group (GIS) Autism /NDD (Aviesan), as well as European projects and collaborations targeting research on sleep trait and state markers in the general pediatric population vs. NDD (Eden cohort, Elfe French birth Cohort, Lifecycle European birth cohort consortium, Longitools, etc). Participatory research projects with users and family associations are currently ongoing, with institutional support from INSERM. Early onset sleep disturbances have been shown to be associated with cognitive and behavioural symptoms in the NDD range and their developmental trajectories (Reynaud et al, Sci Report 2018, Reynaud et al, Sleep Med 2018; Reynaud et al, JSR 2018; Murcia et al, JSR, 2019; Reynaud et al, Behav Sleep Med, 2020). In adolescents and young adults with ADHD, EDS phenotypes have been extensively described (Bioulac et al, Sleep Med, 2017; Bioulac et al, JAD, 2020; Bioulac et al, Front Psy 2020.). On a methodologically, actigraphy has been validated versus polysomnography in several populations of children (autism, ADHD, narcolepsy type I, healthy children, and babies/newborns <2 year-old; ongoing). In addition, a digital sleep log has been developed, with specificities related to sleep-wake rhythms in children, for use across multiple French cohort studies (Oniros kids, C Schroder, E Reynaud). An important issue is also the validation of questionnaires in this specific young population, such as the hypersomnolence scale (his) within the population of children and adolescents (S Bioulac).

Several sleep interventions have demonstrated their efficacy in psychiatric disorders and improved health outcomes (Lederman et al, J Psy res, 2019). For example, cognitive behavioral therapy for insomnia (CBT-I) has shown efficacy for the treatment of depression and anxiety and improves sleep duration and insomnia symptoms (Morin et al, JAMA, 2009; Taylor and Pruiksma, Int Rev Psy, 2014). The CBT-I is a grade A treatment which is further studied in several centers of our psychiatric research group (P Philip and JA Micoulaud-Franchi, PA Geoffroy and J Maruani, Y Dauvilliers and R Lopez, C Schroder and P Bourgin, etc). For instance, Lopez and colleagues validated the first French eCBT-I intervention to improve insomnia disorder in comparison to minimal psychoeducation therapy (Lopez et al, Front Neurol, 2019). Light therapy has been shown to be effective in depressive episodes, for unipolar and bipolar disorders with or without seasonal pattern, with a decrease in depressive symptomatology and an improvement of sleep (Geoffroy et al, Sleep Med Rev, 2019), especially in patients with sleep phase delay or insomnia (Khalifeh, Saudi Med J., 2017; Maruani and Geoffroy, Front Psy, 2019). Light therapy and the study of phototransduction led to several key publications with an international expertise of our research group (P Bourgin and C Schroder, C Gronfier, PA Geoffroy and J Maruani, etc). Geoffroy PA, Schroder CM, E Reynaud and P Bourgin demonstrated that light therapy can be proposed as a first-line antidepressant strategy in depression, with no superiority of antidepressants among light therapy and a clear superiority of the combination over both monotherapies (Geoffroy et al, Sleep Med Rev, 2019). Exogenous melatonin has also demonstrated efficacy on insomnia in adults and children (Buscemi et al, J Gen Intern Med, 2005; Ferracioli-Oda et al, Plos One, 2013), on delayed sleep phase disorder (van Geijlswijk et al, 2010), and also on sleep onset latencies and total sleep time quality (Ferracioli-Oda et al, Plos One, 2013), including patients with psychiatric and neurodevelopmental disorders (Maras et al, Journal of Child and Adolescent Psychopharmacology, 2018; Schroder et al, JADD, 2019; Geoffroy et al, Encephale, 2019). Melatonin is an important therapeutic axis with an increasing interest and many several physiological effects that are examined by our research group with recognized international expertise with several publications (Maras et al, Journal of Child and Adolescent Psychopharmacology, 2018; Schroder et al, JADD, 2019; Veyrier et al, Encephale, 2020) and French guidelines (Geoffroy et al, Encephale, 2019). Other strategies are tested by the group such as the neurofeedback (led by Micoulaud Franchi JA), which offer promising therapeutics strategies to influence the electrical activity of the brain and integrate clinical neurophysiological markers (Micoulaud-

Franchi et al, *Neurophysiol Clin*, 2020), in particular for insomnia and hypersomnolence disorders. These interventions could be assessed and potentially used as strategies to prevent conversion toward full mental disorders, and help vulnerable or at-risk individuals to adapt to changing external or environmental conditions with critical changes over time. Our group contribute to several international tasks force in bipolar disorders with the ISBD with published consensus regarding practice recommendations on chronotherapy and chronobiology in bipolar disorders (Gottlieb et al, *Bipolar Disord*, 2019) and about circadian measurement tools for use in mood research and practice (Murray et al, *Bipolar Disord*, 2020). Joint Italian and French expert guidelines about the use of melatonin in neuropsychiatric disorders should be published during 2021, and follow the French guidelines published in 2019 (Geoffroy et al, *Encephale*, 2019).

Lastly, from an nosological point of view, the interaction between mental and sleep disorders, offer the opportunity to better define sleep disorders in the evolution of medical classification. Indeed, as it was conducted for mental disorders, sleep disorders classification should be evaluated in term of the reliability, validity and practicality of the different “Clinical manifestation” criteria. Moreover, it is necessary to develop a consensual terminology of sleep manifestation in sleep medicine and a standardized clinical interview to capture it, and to evaluate the relationship of sleep disorder category with a sleep dysfunction or a physiological dysfunction occurring during sleep. The large amount of methodological and epistemological literature developed in the field of psychiatry could be cross-fitted with the challenge of sleep disorder, to better investigate the way to rigorously operationalize the conceptual framework for the evolution of sleep disorders diagnostic criteria. The use of data-driven analysis based on bioinformatics methodologies or ontological analysis could be useful to better build the structure of the sleep disorders diagnostic criteria.

A new French network has been organized since 2018 coordinated by C Schroder and PA Geoffroy named “SoPsy” (sleep and biological rhythms in psychiatry) of the French Association of Biological Psychiatry and Neuropsychopharmacology (AFPN) and the French Society for Sleep Research and Medicine (SFRMS). This expert network includes 36 centers who contribute to a national cohort about depression (with two grants from the SFRMS and from Fondation de l’Avenir) and defined a common dataset with standardized questionnaires. The SoPsy network with the research group will allow to better structure the psychiatry research axis and participate in national, European and international funding programs and open calls.

V. Basic research

Basic research is playing a critical role in opening new avenues of investigation and is well represented in the Sleep Research Group. For example, the Sleep and emotional memory team led by G Girardeau at the Institut du Fer-à-Moulin (Paris) studies the mechanisms for the processing of emotions (emotional memory, emotional regulation) during sleep. To do so, they use *in vivo* large scale electrophysiological recordings and optogenetics in the rat, to study and modulate the hippocampus and amygdala neuronal networks involved in such processing (Girardeau et al, *Nature Neuroscience*, 2017). The Forgetting team in the CNRL, Lyon, led by P Salin and G Malleret showed that paradoxical sleep plays a major role in consolidation of remote long-term emotional memory in mice (Rosier et al, *Sleep*, 2018), and also induces a long-term reorganization of neuronal activity in emotion related limbic areas. In an interesting parallel, the team PAM (Perception, Attention, Memory), in the same institute, (P Ruby and A. Caclin) observed in humans that dreams attenuate the emotional intensity of waking-life memories (Vallat et al, *PlosOne*, 2017). These projects aim to understand sleep-dependent plastic processes involved in normal and pathological (PTSD, anxiety) conditions. The MOBs team (Memory, Oscillations and Brain states) in ESPCI Paris (K Benchenane) studies the brain states related to the different brain oscillatory modes and their role in memory processing, based on *in vivo* and *ex-vivo* approaches (Lavilléné et al, *Nature Neuro*, 2015; Bagur et al, *Plos Biology*, 2018; Varin et al, *J Neuro*, 2015). An important part of their work done in the past years has been focused on a better characterization of sleep oscillatory processes with massive recording methods. This characterization can thus be extended to other

wake-related brain states such as the ones observed during fear learning (Bagur et al, *Nature comm*, in press). They also constantly develop the use of brain-computer interface to demonstrate causality between neuronal activity and behavior. Sleep problems are frequently associated with mood disorders including those with recurrent depression or anxiety. However, the neuronal network driving sleep abnormalities in mood disorders remains largely unknown. The group led by V Fabre (Institut de Biologie Paris Seine) investigates the 5-HT neurons of the raphe nuclei, known to promote behavioral arousal. Part of these neurons express VGLUT3, the vesicular glutamate transporter type 3, which allows 5-HT neurons to use, in addition to 5-HT, glutamate as a neurotransmitter. By using chemogenetics and conditional gene inactivation approaches, they demonstrate that the effects of psychological stress on sleep are mediated by raphe VGLUT3 neurons. In the Center for Interdisciplinary Research in Biology (College de France, Paris) Armelle Rancillac and her collaborators have provided new insights regarding the orchestration of sleep regulation by the release of serotonin (5-HT), showing that ventrolateral preoptic nucleus (VLPO) sleep-promoting neurons express different subsets of 5-HT receptors to play either a permissive role, or an executive role in the induction and maintenance of sleep (Sangare et al, *Neuropharmacology*, 2016). The team also demonstrated in the VLPO that astrocyte-derived adenosine differentially adjusts local energy supply to neuronal activity according to sleep-wake cycles (Scharbarg et al, *Sci Report*, 2016). In another study, she demonstrated an anatomical and functional connection between two structures involved in the regulation of slow-waves sleep (Walter et al, 2019).

Sleep and wakefulness are often described as mutually exclusive, all-or-nothing phenomena. However, recent research has shown that the boundary between sleep and wakefulness is rather fluid. In particular, there are moments during the day where local brain networks can show patterns of activity that are reminiscent of sleep and there are moments during the night where local brain networks can show patterns of activity reminiscent of wakefulness. These local intrusions of sleep during waking and of wake during sleep have been termed “local sleep”. The research of T Andrillon, in the Movit team (“Mouvements anormaux et ganglions de la base : physiopathologie et thérapeutique expérimentale”, Institut du cerveau, Paris) focuses on the physiological characterization of these events, using a combination of invasive and non-invasive brain imaging techniques in healthy individuals and patients (Andrillon, *Current Opinion in Physiology*, 2019; Nir et al, *Nature medicine*, 2017). Finally challenging electrophysiological recording in lizards have led the SLEEP team to confirm and extend the existence of two different sleep states in reptiles, providing new concepts on the evolutionary origin of paradoxical (or REM) sleep (Libourel et al, *Plos Biology*, 2018).

This necessarily small overview does not intend to be exhaustive; it nevertheless provides a sampling of the diversity and wealth of approaches present in the group. Basic research is of course complementary to more clinically oriented research areas. Several teams are conducting both in translational research projects (see II. Links between the clinical and pre-clinical research).

B. European implementation of the Sleep Research Group

The main goal regarding the different research activities is to establish and develop an international network targeting to initiate and conduct basic research and large trials and also aiming to improve European funding perspectives:

I. Interventional trials at the European and international level

Members of the Sleep Research Group have actively participated (> 200 patients included) and were members of the steering committee of the SERVE-HF European study which is the largest RCT to date in the sleep apnea field.

They also act as principal investigators (PIs) both at the national and European level for the Pitolisant study addressing residual sleepiness in OSA. Numerous Pitolisant studies to manage EDS in narcolepsy, Parkinson' disease and OSAS have been coordinated by the different members of the INI network at the European level (Studies funded by Bioprojet).

Pr. Pépin (Laboratoire HP2, INSERM U 1300, UJF Grenoble) is Principal Investigator for the largest telemedicine study in sleep apnea (Funded by a consortium of 9 home care providers and 4 CPAP manufacturers).

Pr. Gagnadoux (INSERM UMR 1063, Université d'Angers) is the coordinator for France of the Post Market EliSA study evaluating the GenioTM (Nyxoah, Belgium) hypoglossal nerve stimulation system for the treatment of OSA.

Pr. Pépin is a member of the International Collaboration of Sleep Apnea Cardiovascular Trials (INCOSACT) Researchers. It is a newly formed collaboration of investigators interested in conducting randomized controlled clinical trials of Sleep Apnea treatment interventions.

Some members (Pr Dauvilliers, Dr Barateau, Dr Lopez, pr Arnul, Pr Monaca, Pr Franco, Pr Philip...) of the Sleep Research Group were members of the EUNN (European Narcolepsy Network) with several EU projects to better define diagnosis and management of narcolepsy and rare hypersomnias. We also participated in most of the largest RCTs in the treatment of narcolepsy and idiopathic hypersomnia (Pr Dauvilliers International PI for most of these trials, pitolisant adulte et enfant, sodium oxybate enfant, FT218, JZP 258, JZP 110 and orexin receptor agonists).

The Dream study was a European study for validation of detection of sleep apnea via pacemakers devices and software (Funded by Sorin, Also ANR TecSAN Pasithea). Another international collaborative study is ongoing on the same topic (Funded by Boston Scientific).

Regarding non-invasive ventilation (NIV), The Grenoble team is involved in the European registry of non-invasive ventilation and there is an on-going study comparing ambulatory versus in-hospital initiation of NIV (UK, France, Switzerland, US funded by Philips).

This demonstrates that network members are in a position to lead and conduct international interventional trial for innovative drugs, devices and also to validate new clinical pathways for diagnosis and e-health.

II. Cohorts: A network at the national and international level

The Sleep teams of the group are already recognized and have scientifically productive national cohorts (OSFP, Proof, Cohorte des pays de Loire, Cohorte des 3 cités, AuBe, ELFE, KANOPEE). The common sleep phenotype will be used to create a merged multi-cohort project using pooled data. This consortium of researchers with strong expertise in different fields of sleep medicine will enable new ground-breaking research to be conducted.

At the European level the Pr. Pepin team is a significant contributor to the European Sleep Apnea Cohort (ESADA) which is a multi-center, multinational study, prospectively recruiting subjects attending sleep laboratories across Europe (> 11,000 OSA included).

Finally, Sleep researchers from around the globe have formed the Sleep Genetics international consortium (SAGIC), and more recently the Insomnia Genetics Consortium. This unique collaboration comprises sleep disorders and cardiovascular experts from the US, Iceland, Germany, France (Grenoble, Montpellier), Australia and Brazil.

We are following the 3C study, a cohort study focusing on dementia and vascular signs in France with more than 9 000 participants above 65 years old included at baseline with follow-up each two years. All subjects had a clinical sleep evaluation and a subgroup (from Montpellier) also underwent a polysomnography assessment.

The reference center for Narcolepsy in Montpellier coordinated by Pr. Dauvilliers runs several research projects on hypersomnia at the regional (Somnobank: A clinical and biological cohort on hypersomnolence, performed in Montpellier), national (i.e. a dedicated French cohort on narcolepsy and idiopathic hypersomnia is currently being discussed at the national level in link with PNMR3 and related ANR grant) and European levels. A common European database on narcolepsy (EUNN) has been set up in the last few years and now functions on a routine basis. The French Sleep network will provide a large number of children and adult patients to the database and reinforce the position of the French team within the EU to conduct innovative research projects.

The KANOPEE cohort recently initiated in Bordeaux cover the french population with 14000 users of dCBT to prevent insomnia, fatigue and mental disorders. Connections with the University of Bordeaux and CHU of Bordeaux are established to reinforce the tracking , treatment and follow up of KANOPEE users via a network of sleep centers over France (SFRMS partnership).

C. OBJECTIVES

The Goals of the Sleep Research Group will be to increase the knowledge of the pathophysiology of central hypersomnia, sleep apnea syndrome, psychiatric disorders and behavioral somnolence/chronobiological disorders and its consequences, to find new treatments to fight against the disease symptoms, to recruit more patients in the phase I to III trials and cohorts, and finally to increase the number of collaborative publications related to the different domains included in the network (better understand to better treat).

I. Central hypersomnia specific objectives

Better understand:

- Identify the neuronal mechanisms responsible for inducing wakefulness, slow wave (NREM) and REM sleep. Although a number of populations of neurons inducing wakefulness, NREM and REM sleep have been identified, more certainly exist. Further each population plays a specific role in each state and it needs to be determined. In addition, the mechanisms responsible for the activation of the W, NREM and REM sleep neuronal systems at states transitions remain to be identified. Finally the function of sleep is still unclear and more studies are needed at the molecular, cellular and systems levels to answer this key question in particular with regards to sleep pathologies.
- Merge the different clinical cohorts already existing in the field of central hypersomnolence disorders to provide strong and wide-ranging longitudinal data. Reinforce on-going research on longitudinal studies of circadian and sleep disturbances in narcolepsy, idiopathic hypersomnia, kleine levin syndrome, autism and other neuro-developmental disorders.
- Determine the potential underlying pathophysiological mechanisms (through biological, genetic, immune, morphological, and neurophysiological assessments) involved in the relationship between hypersomnia and comorbid disorders such as mental health, neurodegenerative and cardiovascular disorders.
- Create a unique hypersomnia phenotype and biological databank with longitudinal data (Filière de soins National Reference Center for Rare Diseases "Hypersomnie") in order to participate in systematic genome scanning, to investigate the weight of environmental risk factors (H1N1-AS03 vaccine), to study the impact of hypocretin deficient narcolepsy on the cardiovascular system, metabolism, cognition, decision-making, addiction, and pain, and to identify other biomarkers in the field of central hypersomnias (first narcolepsy but also idiopathic hypersomnia and kleine Levin syndrome).

To better treat:

- Develop new Therapeutics of Excessive Daytime Sleepiness, based on innovative findings from physiopathology and animal models, and combined therapies and personalized medicine.
- Develop novel therapies targeting the orexin system and its projections on the histamine system, but also the norepinephrine, the dopaminergic (solriamfetol), the serotonergic and GABA systems, and modulator of drugs such as modafinil (targeting intercellular communication, connexins, THN02) for hypersomnia disorders including narcolepsy.
- Immune-based therapies at early stages of narcolepsy-cataplexy to prevent the loss of hypocretin (i.e.). Inverse agonist of the H3 receptor (Pitolisant), dopaminergic-norepinephrine drugs (solriamfetol) hypocretin agonists, hypocretin cell transplantation and gene therapy also need to be developed for patients with narcolepsy.

II. Sleep apnea syndrome specific objectives**Better understand:**

To identify pathways that mediate occurrence and cardiometabolic consequences of the common disorder obstructive sleep apnea to facilitate development of novel therapeutic approaches.

- the neuronal mechanisms responsible for motor control of the upper airway musculature during NREM and REM sleep using up to date methods such as optogenetic.
- Evaluate the deleterious effects of combinations of sleep associated disorders (i.e. sleep deprivation and sleep apnea; RLS and sleep apnea, narcolepsy and periodic leg movements etc.), and demonstrate whether or not a combination of sleep disorders leads to a synergistic risk and then requires specific approaches (see below personalized medicine).
- Evaluation in sleepy patients whether the treatment of EDS will modify cognitive, metabolic and cardiovascular functions.
- Initiate and validate new simplified diagnosis strategies in at risk populations (expected patents, innovation and valorization).

To better treat:

- Develop new Therapeutics of Excessive Daytime Sleepiness for OSAS patients (behavioral, pharmacological and non-pharmacological i.e. light) based on innovative findings from physiopathology and animal models, and combined therapies and personalized medicine in the field of excessive daytime sleepiness and nocturnal sleep breathing disorders.
- Continuous positive airway pressure impact on cardiovascular and metabolic outcomes is limited. Complex interventions including combined therapies should be implemented in large clinical trials (CPAP plus exercise plus life style intervention) to potentiate its impact.
- Validate new drugs increasing muscle upper airway activity and drugs stabilizing ventilation by manipulating arousal threshold.
- Develop new dental appliances and stimulators (stimulation of hypoglossal nerve) to treat OSAS (alternative therapeutics for non-compliant CPAP patients).

III. Behavioral somnolence specific objectives/ chronobiology

Better understand:

- the basic mechanisms responsible for sleep homeostasis. The molecular and cellular state of the cortex during long lasting waking period and the mechanisms taking place at that level during recovery sleep.
- To study the inter-individual vulnerability to sleep loss in healthy subjects and patients with central hypersomnia to understand the links between EDS, the circadian timing system, sleep history, sleep hygiene, metabolism, cardiovascular risk and cognitive impairment.
- To use existing (i.e. Wake EEG, polysomnography and neurophysiological daytime sleep/vigilance tests) and to identify new biomarkers to get normative data of alertness in healthy subject, to evaluate in real time the impact of sleepiness on performance aiming at reducing the risk accident, to specify the phenotype of EDS in several conditions, as well as compensatory systems (e.g. hyperactivity), and to study the consequences of EDS in patients.
- The effects of light and the consequences of poor light hygiene (inappropriate light exposure in terms of timing, intensity and spectrum) on sleep, circadian alignment and alertness.
- Sleep deprivation and sleep extension protocols in healthy subjects to categorize vulnerability to sleep loss and new markers predicting the vulnerability to sleep loss.
- The consequences of sleep loss on nutrition, cardiovascular and immune functions
- The epidemiology and the determinants of sleep loss quantified by objective and standardized methods in different populations.

To better treat:

- Find new treatments based on the knowledge acquired on sleep homeostasis.
- Test the combination of anti-orexin and/or CBT treatment for insomnia treatment.
- Test the efficacy of light (i.e. lighting strategies) and chronobiotic treatments (i.e. melatonin agonists) as treatment of insomnia and poor sleep hygiene.
- Develop new non pharmacological therapies based on immersion in virtual environment and internet based CBT to treat sleep complaints.
- Develop information and decision systems to improve treatment of sleep disorders
- Develop education and prevention of sleep loss in shift and night workers, in adolescents and young adults, in patients with chronic diseases.

IV. Neurodevelopmental and psychiatric disorders

Better understand:

- Determine the potential underlying pathophysiological mechanisms (through genetic, biological, neuroimaging, neurophysiological and ecological momentary assessments) involved in the relationship between sleep and biological rhythm alterations and neurodevelopmental and psychiatric disorders.
- Determine and better characterize relationships between sleep apnea syndromes, central hypersomnias and circadian rhythms disorders and psychiatric disorders

- Better understand longitudinal and neurodevelopmental trajectories, in particular for NDD, in relation to respiratory and sleep disorders.
- Identify more homogeneous subgroups of patients within these very heterogeneous psychiatric entities through sleep and circadian biomarkers (depression, suicide, autism, psychotic disorders, ADHD, Anxiety disorders, addictive disorders, etc).
- Create a unique national psychiatry databank (SoPsy) with cross-sectional and longitudinal data in order to participate in National, European and international projects.
- Develop expertise in terms of multimodal and AI/machine approaches to examine digital and big data

To better treat:

- Develop chronotherapies specific to neurodevelopmental and psychiatric disorders and clarify modalities of use of existing ones (for instance bright light therapies, melatonin, wake therapy, dark therapy, CBT-I, TIPARS, wake drugs, etc).
- Better characterize response to psychotropics and hypnotics using sleep and biological rhythm biomarkers
- Personalized treatments depending on sleep and rhythm characteristics using clinical and biological markers.
- Personalized strategies by considering the neurodevelopment, age, gender, psychiatric and addictive comorbidities.
- identify new treatments in psychiatry thanks to a better knowledge of sleep homeostasis and biological rhythm alterations within these disorders.

V. Basic research

Better understand:

- Develop common methods to facilitate the collaborations between groups. For example, formatting and scoring EEG and LFP data. The involved teams are working on establishing a file template featuring the localization of electrodes and all recording parameters in a standardized manner. Regarding the scoring, the objective is also to develop common methods and improve them.
- Dissect the bidirectional interactions between contextual issues - behavior, light, time of day, food, metabolic and immune status - and vigilance states in field work as well as in controlled laboratory conditions and animal models.
- Identify so far little explored non-neuronal brain mechanisms, involving the blood-brain-barrier, hemodynamics, and neuro-glial interactions
- Identify biomarkers of vigilance states and sleep debt using animal models, electrophysiology and molecular genetic approaches
- Develop the networking between investigators with different expertise through regular meetings and workshops. Facilitate the training of investigators new to the field of basic sleep research. Develop connections with clinical research through collaborations. Understanding the basic mechanisms

underlying sleep-wake regulation and function is obviously crucial to all the clinical objectives of the GDR.

D. GENERAL ORGANISATION

The Sleep Research Group will rely on teams of CNRS or INSERM Units plus university teams (*fig. 1*). Each partner of the group will work in close relationship regarding their own domain of expertise (rare central hypersomnia, SAS, behavioral somnolence and neurodevelopmental and psychiatric disorders). Each domain of expertise will be coordinated by a well known sleep researcher in order to develop each sub community. Since the previous GDR (3737) we have added two significant specific communities (basic research and psychiatry) and we believe this strategy will allow us to expand Sleep research among new communities. A special attention will be dedicated to European projects through a specific co-coordination assured by PH Luppi, actual president of the European Sleep Research Society. Funding is a key issue for Sleep research and we hope to reinforce European funding via this co-coordination.

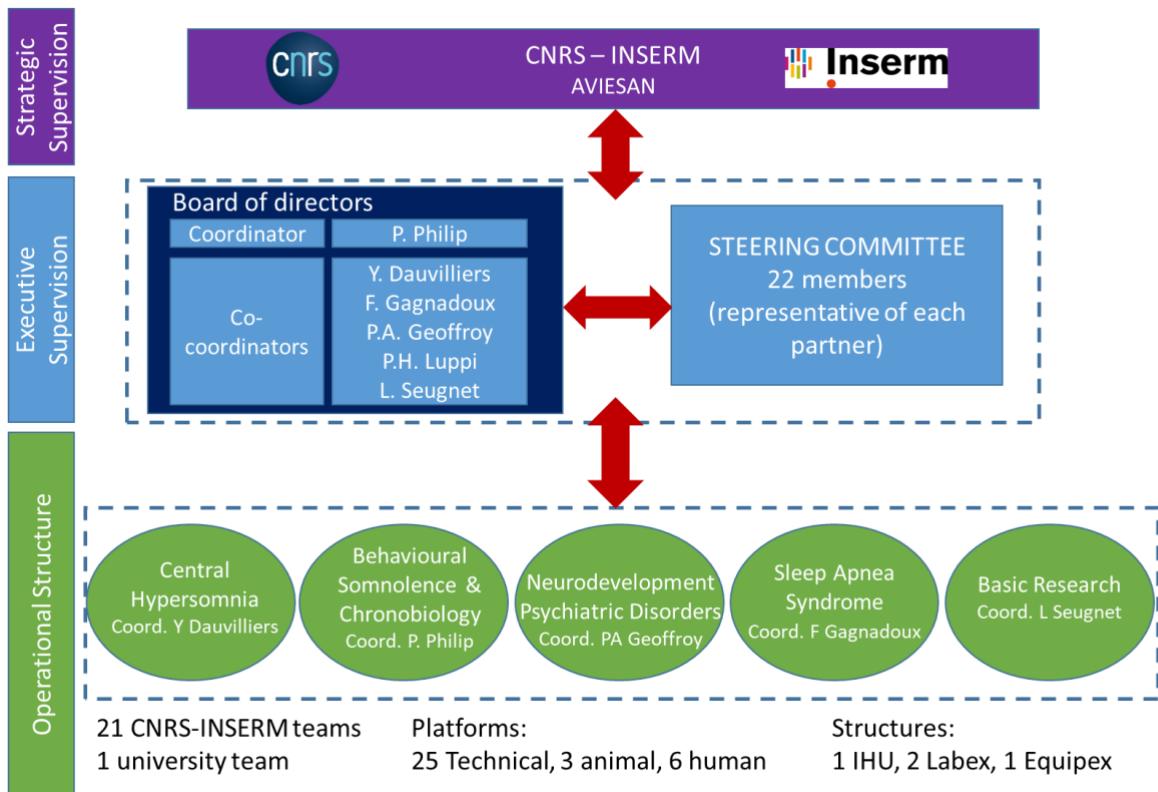
Governance (fig.2)

A Steering Committee, with representation of each of the 22 teams of the Sleep Research Group helped by external invited members (academic and industrial projects partners, CNRS, INSERM, AVIESAN representatives), will provide advices and scientific guidance of the research group program; evaluate new projects and progress reports. A first meeting will take place within the first 3 months of setting-up the Sleep Research Group. Then a bi-annual meeting of the Steering Committee will be scheduled. As for the previous GDR an annual meeting will allow to follow the progress made in grant obtention and new research programs.

Board of directors

The board of directors is composed of the Sleep Research Group coordinator (Pr P Philip, coordinator of the GDR and of the behavioral somnolence/chronobiology theme) and the 5 co-coordinators (Pr. Dauvilliers, coordinator of Central hypersomnia theme; Pr. Gagnadoux, coordinator of SAS theme, Dr. Laurent Seugnet, coordinator of basic science teams and projects, Dr Geoffroy, coordinator of the neurodevelopmental and psychiatric disorders theme), Dr Luppi, European coordination).

The board of directors will establish a link between the Steering Committee and the operational management. Semestrial meetings of the board of directors will be organized: conference call or face-to-face meetings. The board of directors will draft an annual progress report for presentation to the steering committee.



Appendix 1 : SLEEP RESEARCH GROUP TEAMS

Central Hypersomnia

Equipe: **Neuropeps**

Représentant: Yves DAUVILLIERS

Inserm U1298, Institut des neurosciences de Montpellier (INM)

Tutelles : INSERM, Université Montpellier

Directeur : Pr S LEHMANN

Responsable d'équipe : Yves DAUVILLIERS

Equipe **END-ICAP** « Handicap neuromusculaire : Physiopathologie, Biothérapie et Pharmacologie appliquées »

UMR 1179

Représentante : Maria Antonia QUERA SALVA

Tutelle : Inserm, Université de Versailles Saint-Quentin-en-Yvelines

Responsable d'équipe : Frédéric LOFASO

Equipe **Movit** « Mouvements anormaux et ganglions de la base : physiopathologie et thérapeutique expérimentale »

Représentante : Isabelle ARNULF

Institut du Cerveau de Paris

INSERM U 1127/CNRS UMR 7225

Tutelles : INSERM – CNRS – UPMC Paris 6

Directeur : Alexis BRICE

Responsable d'équipe : Marie VIDAILHET

Equipe **WAKING** (Physiologie intégrée du système d'éveil)

Représentant: Jian-Sheng LIN and Laurent SEUGNET

Centre de Recherche en Neurosciences de Lyon (CRNL)

CNRS UMR5292 - INSERM U1028

Tutelles : INSERM– CNRS – Université Lyon 1 – Université de Saint-Etienne

Directeur : Olivier BERTRAND

Responsables d'équipe : Jian-Sheng LIN and Laurent SEUGNET

Behavioural Somnolence & Chronobiology

Equipe **GENPPHAASS**

Représentant: Pierre PHILIP

SANPSY (Sleep, Addiction and NeuroPSYchiatry)

CNRS USR 3413

Tutelles : CNRS - Université de Bordeaux

Directeur et responsable d'équipe: Pierre PHILIP

Équipe « **Lumière, rythmes, homéostasie du sommeil et neuropsychiatrie** »

Représentant : Patrice BOURGIN

Institut des Neurosciences Cellulaires et Intégratives (INCI)

UPR3212

Tutelle : CNRS

Directrice: Marie-France BADER

Responsable d'équipe : Patrice BOURGIN

Equipe **COMETE** « Mobilité, Vieillissement, Pathologie, Santé»

Représentant: Damien DAVENNE

INSERM UMR-S U1075

Tutelles : INSERM, Unicaen

Directeur : Damien DAVENNE

Equipe **VIFASOM** (SOMmeil Fatigue Vigilance et santé publique)

Représentant : Damien LEGER

EA7330

Tutelle : Université Paris 5

Responsables : Damien LEGER et Mounir CHENAOUI

Neurodevelopmental and Psychiatric Disorders

Equipe **NeoPhen**

Représentant: Pierre Alexis GEOFFROY

InsERM U1141, Unité NeuroDiderot, Axe Biomarqueurs du sommeil et des rythmes biologiques dans les troubles psychiatriques

Tutelles : INSERM, Université de Paris

Directeur : Pierre GRESSENS

Responsables d'équipe : JC DELCLAUX, B MATROT

Équipe **EAROH** « Recherche sur les déterminants précoce de la santé »

Représentante : Sabine PLANCOULAIN

InsERM U1153, Centre de Recherche en Épidémiologie et Statistiques (CRESS),

Université de Paris, INRAE

Directeur Philippe RAVAUD

Responsable de l'équipe : Marie-Aline CHARLES

Sleep Apnea

Equipe “**Syndrome d'apnées hypopnées obstructives du sommeil (SAHOS) et dysfonction endothéliale**”

Représentant : Frederic GAGNADOUX

Stress Oxydant et pathologies métaboliques (SOPAM)

UMR INSERM 1063

Tutelles : INSERM, Université d'Angers

Directeur: Dr Ramaroson ANDRIANTSITOHAINA

Laboratoire HP2 « **Hypoxie et Physiopathologies cardiovasculaires et respiratoires** »

Représentant: Jean-Louis PEPIN
INSERM U1042 /UGA
Tutelles : INSERM, Université Joseph Fourier Grenoble
Directeur : Patrick LEVY
Responsable d'équipe : Jean-Louis PEPIN

Equipe **Sainbiose** «Santé Ingénierie Biologie Saint-Etienne»
Représentant : Frédéric ROCHE
INSERM U1059
Tutelle : INSERM, Université Jean Monnet Saint-Etienne
Responsable d'équipe: Laurence VICO

Equipe « **Troubles cognitifs dégénératifs et vasculaires** »
Représentant : Christelle MONACA
INSERM U1171
Tutelles : INSERM, Université de Lille 2
Responsable d'équipe : Régis BORDET

Basic research

Equipe **MOBS** "Memory Oscillations and Brain States"
Représentant : Karim BENCHENANE
Laboratoire Plasticité du Cerveau
CNRS MMR 8249, ESPCI Paris, Université Paris Science Lettre (PSL)
Tutelles : CNRS, ESPCI ParisTech
Directeur : Thomas PREAT
Responsable d'équipe : Karim BENCHENANE

Equipe **Sleep and emotional memory**
Représentante : Gabrielle GIRARDEAU
Institut du fer à moulin
UMR-S 1270
Tutelles : INSERM, Université Sorbonne
Directrice : Fiona FRANCIS
Responsable d'équipe: Gabrielle GIRARDEAU

Equipe **SLEEP** (Physiopathologie des réseaux neuronaux du cycle veille-sommeil)
Représentants : Christelle PEYRON - Pierre Hervé LUPPI
Centre de Recherche en Neurosciences de Lyon (CRNL)
CNRS UMR5292 - INSERM U1028
Tutelles : INSERM – CNRS – Université Lyon 1 – Université de Saint-Etienne
Directeur : Olivier BERTRAND
Responsables d'équipe : Christelle PEYRON and Pierre-Hervé LUPPI

Equipe **PAM** (Perception, Attention et Mémoire)
Représentante : Perrine RUBY, Karine SPIEGEL
Centre de Recherche en Neurosciences de Lyon (CRNL)

CNRS UMR5292 - INSERM U1028

Tutelles : INSERM– CNRS – Université Lyon 1 – Université de Saint-Etienne

Directeur : Olivier BERTRAND

Responsables d'équipe : Anne CACLIN & Perrine RUBY

Equipe FORGETTING

Représentant. Paul SALIN

Centre de Recherche en Neurosciences de Lyon (CRNL)

CNRS UMR5292 - INSERM U1028

Tutelles : INSERM– CNRS – Université Lyon 1 – Université de Saint-Etienne

Directeur : Olivier BERTRAND

Responsables d'équipe : Gaël MALLERET et Paul SALIN

Equipe: « Neuropharmacologie des VGLUTS »

Représentante : Véronique FABRE

Neuroscience Paris Seine (NPS), Institut de Biologie Paris Seine (IBPS)

Sorbonne Université, UPMC UM 119, INSERM U1130, CNRS UMR 8246

Tutelles : CNRS - INSERM – Sorbonne Université

Directeur : Hervé CHNEIWEISS

Responsables d'équipe : Stéphanie DAUMAS et Nicolas PIETRANCOSTA

Equipe « Interactions neurogliales dans la physiopathologie cérébrale »

Représentant: Armelle RANCILLAC

CNRS UMR 7241 / Inserm U1050

Center for Interdisciplinary Research in Biology – CIRB

Tutelles : CNRS - INSERM

Directrice: Marie-Hélène VERLHAC

Responsable d'équipe : Nathalie ROUACH

Equipe Mémoire & Oubli,

Représentante: Géraldine RAUCHS,

Unité 1077 « Neuropsychologie et Imagerie de la Mémoire Humaine »,

Tutelles : Inserm-EPHE-UNICAEN

Directeur : Pr. F EUSTACHE.

Attention : changement de laboratoire de rattachement au 1er janvier 2022 : Inserm U1237, PhIND

"Physiopathology and Imaging of Neurological Disorders", directeur : Pr D. VIVIEN

APPENDIX 2: BIBLIOGRAPHY

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