Neuroengineering for Exploring and Repairing the Brain (NeuroPSI-Chen Institute Joint Conference on Brain, Behavior & Beyond)

This year marked the second annual NeuroPSI-Chen Institute Joint Conference on Brain, Behaviour, and Beyond. The event was hosted by the Paris-Saclay Institute of Neuroscience (NeuroPSI) and generously funded by the Tianqiao & Chrissy Chen Institute (TCCI). This year's conference explored multiple facets of neuroengineering at the interface between electronics, robotics, and cellular biology, providing promising perspectives for repairing sensorimotor and mental health deficits. The event was a tremendous success and showcased the latest cutting-edge research through a series of symposia. These symposia featured invited plenary speakers worldwide, followed by succinct short talks and poster sessions providing a unique opportunity for networking and exchanging ideas.

Day 1: May 16, 2024

The first day of the conference comprised six plenary talks and three short talks spread over two sessions. These sessions spanned from somatosensory-motor restoration to neurotechnologies for psychiatry. The poster presentations were held between the sessions and after the last talk.

Session 1: Somatosensory-motor restoration

Richard Andersen
California Institute of Technology (Caltech), USA

“Unlocking movement: helping paralyzed people with brain-machine interfaces”

Professor Richard Andersen began his talk with a thought-provoking statement, "paralyzed people still think about moving." If one could decode a paralyzed person's thoughts into a prosthesis movement, one could regain control and independence. This is the goal of Richard and his team at Caltech. They are developing a neural prosthesis that records a patient's nerve impulses in the brain, that are decoded as intentions by a computer which translates them into movements of a prosthetic limb. This all seemed very futuristic to some people in the audience, but he demonstrated that they were not too far from cracking the code. Richard played a motivational video of his first patient, Eric, whose goal was to drink a beer without his mother's help. In the video, we could see that Eric was able to control a robotic arm to pick up and move a bottle of beer to his mouth, take a refreshing sip, and replace the bottle on the table. This moment was very moving and marked a significant milestone for both Eric and Richard's team. Their computer algorithms can even detect differences at the single-finger level! Their Brain-Machine Interface can decode intentions to move and speak, which can give the voiceless their voice back. If that was not enough, Richard and his team were interested in restoring a patient's 'feeling' by adding touch sensors to a robotic hand, which can provide feedback to the brain with sensory information. The next goal is to make a more dextrous sensation.

Richard Andersen presenting his work on Brain-Machine Interface (BMI) decoding intentions into movement and speech production.

Nicolas Simon
Wandercraft, France

“Exoskeletons for rehabilitation and assistance”

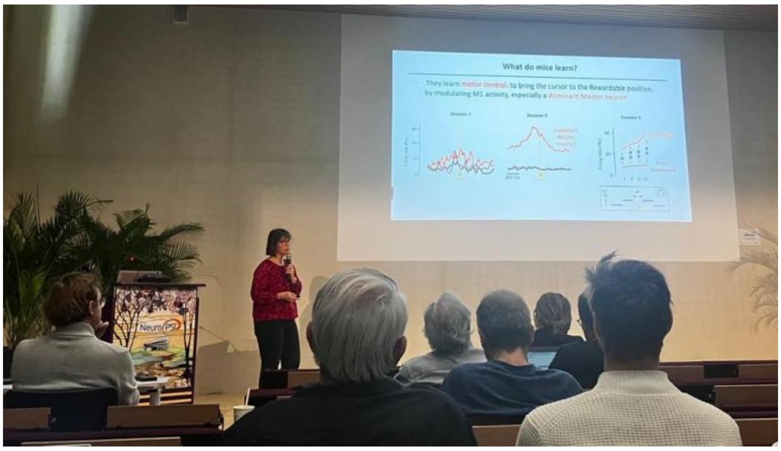
The second plenary talk of the first session was delivered by Nicolas Simon, co-founder and chairman of Wandercraft, located in the Greater Paris Metropolitan Region. His team of engineers designs exoskeletons that aid in the rehabilitation of paraplegic users and enable them to walk again. He took us through the ten-year evolution of their exoskeleton, from humble beginnings to the latest model that has been on the market since 2019. They started their mission in 2013 with their prototype Atalante v2. However, their model was not strong enough to support the user's weight, lacked lower back support making it challenging to balance, and did not generate "natural" walking patterns. Nine years and four more prototypes later, the Atalante X was born, the first auto-stabilised remote-controlled exoskeleton. This version is much more robust, with more flexible leg supports for enhanced degrees of freedom. The back support not only maintains balance in a standing position, but also has sensors to help adjust for bending or stretching movements. Their robotic exoskeleton has been used to rehabilitate paralyzed users by adjusting the percentage of assistance starting at 100% and decreasing resistance with the patient's progression. Their next step is to make the machine's movement faster for more natural mobility and introduce safety mechanisms for urban environments with uneven terrains.

Nicolas Simon presenting the evolution of the exoskeletons enabling paraplegic persons to walk again.

Valérie Ego-Stengel
NeuroPSI, France

"Delivering artificial tactile feedback during Brain-Machine Interface (BMI) skill learning in a mouse model"

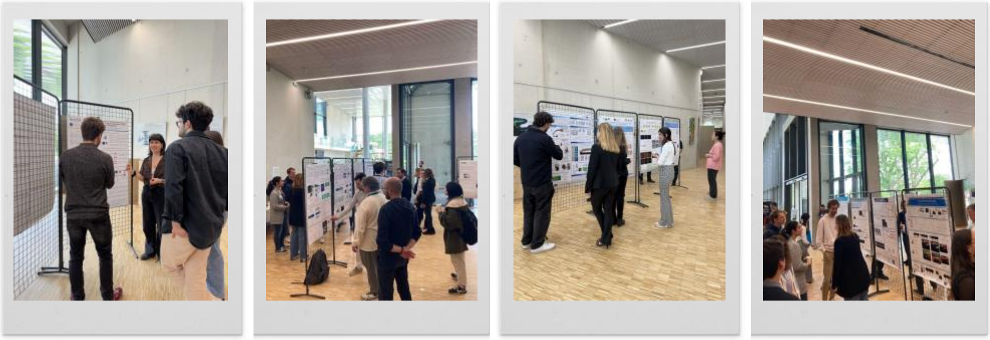
The last plenary talk of the first session was led by Valérie Ego-Stengel, a research director from Daniel Schulz's team at NeuroPSI. She began her talk with a simple question, "How does one learn a skill?" The short answer is through repetition: performing tasks over and over again, receiving rewards when done correctly, and being punished if done incorrectly. In this way, organisms adapt their motor behaviour to sensory inputs from the environment. To study brain activity during learning, Valérie takes advantage of the mouse whiskers, since they provide sensory input from the environment and there is a large part of the brain cortex dedicated to them. She records the activity of individual neurons in the motor cortex (called M1) while the mice receive optogenetic stimulation of a region in the somatosensory cortex linked to whisker movement. The mice then perform a closed-loop learning task. For example, mice learn to move a virtual prosthesis (a cursor) into a rewardable zone (with water available) while receiving information about the state of the prosthesis through optogenetic patterns that activate excitatory neurons. There is an artificial feedback in the primary somatosensory cortex that helps them track the trajectory of the cursor. After different training sessions, the mice's performance is better when feedback provides the position of the cursor in the form of a bar-like photostimulation across the cortical surface. Mice can control a virtual prosthesis by modulating M1 neuron activity, with one of the M1 neurons driving the cursor becoming dominant in terms of activity, thereby increasing the opportunity for rewards. These studies allow us to better understand the cortical mechanisms and the spatial and temporal characteristics of the stimulation patterns most effective for learning motor skills, all of which could have applications in neuroprosthetics. She ended by discussing the current potential direction of the project, which is to control BMI using mesoscale cortical activity.



Valérie Ego-Stengel showcasing the BMI skill learning in a mouse model.

Selected short talks:

The first session consisted of two short talks presented by PhD students Edwin Gatier (Julien Bouvier's team) and Zineb Hayatou (Daniel Schulz's team), both from NeuroPSI. Edwin Gatier's PhD research aimed at investigating the neurons responsible for turning movement in the mouse model. By combining viral and Cre-lox technologies, he identified the V2a neurons as the main controllers of locomotor direction. Zineb Hayatou's talk—a follow-up to Valérie's research—focused on the embodiment of a prosthesis. Using touch input and later direct optogenetic stimulation, Zineb showed that mice shift their gaze towards a threatened "fake paw," suggesting that mice perceive the prosthesis as their own limb. She then replaced the fake paw with a white block and found that the embodiment was not as strong as before, suggesting the importance of the realistic appearance of a prosthesis for patients to perceive as their own. She concluded by discussing their ongoing work on replacing the touch input with optogenetics for their "Promise" neuroprosthesis.



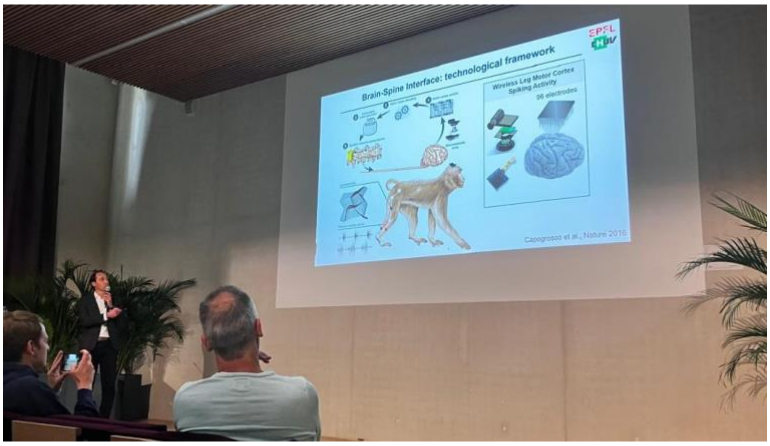
Poster session by PhD students and Postdocs.

Session 2: Neurotechnologies for psychiatry

Fabien Wagner
University of Bordeaux, France

"Neuroprosthetic modulation of distributed brain and spinal cord networks for restoring motor and cognitive function in neurological disorders"

Fabien Wagner opened the second session with a highly captivating talk. He shared his research on how neuronal networks are altered in neurological disorders and spinal injuries, and how neuromodulation can be used to restore their normal motor and cognitive functions. He developed a neuroprosthesis for spatiotemporal stimulation of the spinal cord to restore locomotion in non-human primates, and translated this into a first human clinical trial. He concluded his talk by introducing an exciting new project: expanding the use of neuroprosthetics beyond motor disorders to include memory restoration. The goal of the MEMOPROSTHETICS project is to develop a multi-site brain implant targeting different regions of the brain. The electrodes will record and analyse the neural signals, and in a closed-loop circuit, will respond in real-time with electrical stimulations. In this way, Fabien's team aims to restore learning and memory in a personalised manner for the treatment of memory disorders like Alzheimer's disease and dementia.



Fabien Wagner presenting a technological framework for Brain-Spine Interface in non-human primates.

Mahsa Shoaran
Swiss Federal Institute of Technology Lausanne, Switzerland

"Intelligent neural interfaces for chronic neurological and psychiatric disorders"

Mahsa Shoaran, an Assistant Professor at the Electrical Engineering Institute and Center for Neuroprosthetics (EPFL), gave a talk on the innovations for chronic neurological and psychiatric disorders through intelligent neural interfaces. She discussed novel paradigms for closing the loop in mental illnesses, next-generation intelligent brain-machine interfaces, and AI-enabled closed-loop stimulation for real-time symptom management. She focused on the recent developments in circuit design and machine learning, which are helping the neuroscience community create novel diagnostic and treatment tools for a variety of neurological conditions, including epilepsy, Parkinson's, and Alzheimer's illnesses. Additionally, she showcased low-power and miniaturised systems-on-chips that can record neural activity, identify brain malfunction in real time, and react with therapeutic interventions like neuromodulation. She also highlighted some advancements in circuit designs, the next generation of BMI hardware, as she concluded her lecture.

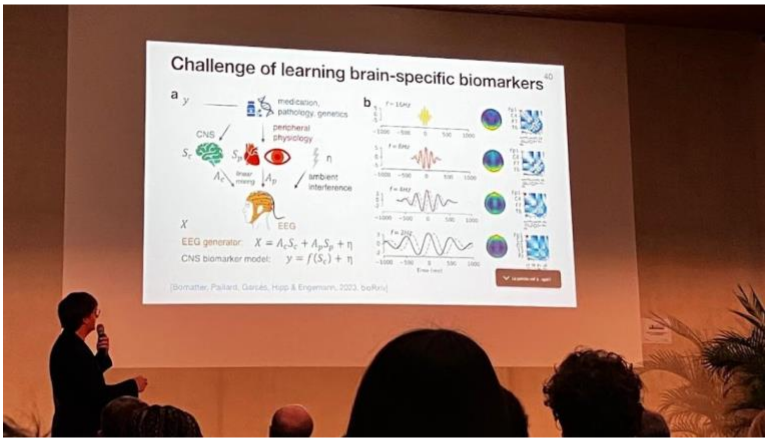
Mahsa Shoaran speaking about intelligent neural interfaces for chronic neurological and psychiatric diseases.

Selected short talk:
PhD student **Laura Lavialle** from our neighbouring NeuroSpin Institute, spoke about improving the emotional regulation of healthy subjects with functional MRI real-time neurofeedback.

Denis A. Engemann
Roche Pharma Research & Early Development in Basel, Switzerland

"From brainwaves to biomarkers: Extending the clinical applications of EEG using machine learning"

Denis Engemann, the "Biomarker and experimental medicine" leader at Roche, was the last speaker of the day and held our attention from beginning to end. He highlighted one of the greatest challenges scientists face: the identification of reliable biomarkers for diseases, as the absence of a biomarker means no drug approval. He advocated for the use of electroencephalograms (EEGs) as biomarkers for neurological disorders. Engemann emphasised several advantages of using EEG biomarkers, including cost-effectiveness, ease of deployment, and the potential for extension by machine learning. He also discussed factors that could lead to breakthroughs, such as innovative instrumentation, a robust ecosystem of vendors, curated datasets, and advancements in signal processing and machine learning. Additionally, Engemann presented GREEN—Gabor Riemann EEG Net—a software that combines wavelet transformations and Riemannian geometry to analyse EEG data. GREEN bridges the gap between machine learning and traditional EEG methods for identifying biomarkers for neurological disorders. Furthermore, GREEN is lightweight, scalable, and extensible, making it a versatile tool for advancing EEG research.



Denis Engemann discussing the challenges of learning brain-specific biomarkers.

After the incredible talks and the extensive topics covered in one day, it was time to end the day with a social gathering at the Golf de Marivaux in Janvry, a small village 15 km from the NeuroPSI Institute.

Day 2: May 17, 2024

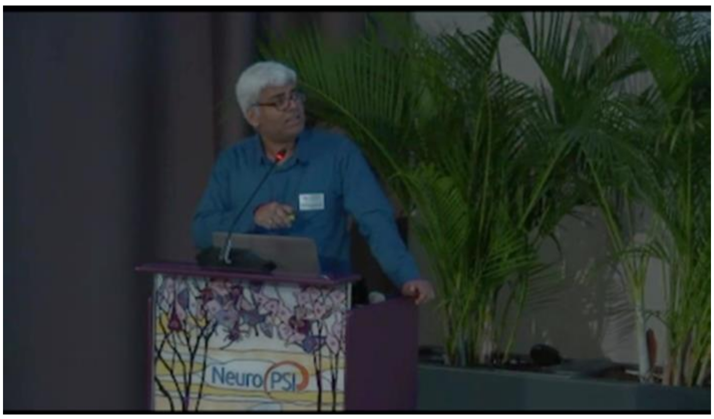
The second day of the conference comprised 5 plenary talks and 4 short talks spread over two sessions. The topics spanned from sensory restoration through AI to cellular and molecular restoration strategies.

Session 3: Sensory restoration through AI

Gopala Anumanchipalli
UC Berkeley, USA

"Speech Neuroprostheses for Restoring Naturalistic Communication"

Gopala Anumanchipalli works at the intersection of Speech Processing, Neuroscience, and Artificial Intelligence, with an emphasis on human speech and assistive technologies. One of his goals is to understand the brain functions underlying fluent speech production and to translate these findings into engineering solutions for individuals who are completely paralyzed and unable to communicate. The biggest challenge in studying speech is the lack of a model organism. To address this, he and his team of researchers recorded brain activity from healthy participants while they read a cue and decoded these recordings into speech. The next challenge was to apply this speech neuroprosthesis to patients with speech disorders. Initially, the speech production was very delayed and sounded unnatural. The machine learning model was then improved to decode more than 1,000 words, resulting in much quicker brain-to-speech communication. Some of his unpublished work demonstrates significant improvements in the speech neuroprosthesis, which now incorporates phonetic and language models, allowing for fluent sentences. He has even managed to mimic the patient's "voice," making the speech less robotic and more reflective of the patient's unique voice. He concluded by discussing the future of communication neuroprostheses, which includes wireless, low-footprint high-density recording, universal vocal tract models, embodied human-centred AI, and closed-loop speech decoding.



Gopala Anumanchipalli talking about the speech neuroprosthesis for restoring naturalistic communication.

Selected short talks:

Jérémie Barral, team leader at the Hearing Institute in Paris, sponsored by Pasteur Institute, spoke about the deficits in spike timing and transmission of auditory information in a mouse model lacking ribbon synapses. This is interesting since it was found that there is a slight increase in auditory threshold and reduced wave I amplitude of the auditory brainstem response (ABR). His team proposed the injection of the Ribeye protein, a major component of the synaptic ribbon, to restore the function. On the other hand, **Antonin Verdier**, a PhD student at Bathellier lab of the Hearing Institute in Paris, spoke about restoring audition. Currently, there is only one treatment for complete hearing loss, the cochlear implant. However, there are limitations such as difficulty hearing conversations in crowds. Antonin's research is part of the Hearlight project which aims to develop an optogenetic cortical implant targeted to the brain instead of the ear. In this way, they can stimulate the auditory cortex to achieve precise auditory restoration.

Fan-Gang Zeng

UC Irvine Medical Center, USA

"Cochlear Implants: The interplay between Basic and Translational Research"

Fan-Gang Zeng is a leading researcher in hearing science and technology, with a primary goal of helping people with hearing impairments hear better. This could be achieved through the use of an electronic device known as a cochlear implant, which can stimulate the auditory nerve and restore hearing for individuals with hearing loss. He also emphasised the importance of making cochlear implants affordable and noted how the price of these devices has dropped over the past decade, thereby benefiting more children. During his talk, Fan-Gang discussed new strategies for restoring hearing capacity, such as ultrasonic and gene therapies, optogenetics, and optoacoustics. He explained how clinical trials using gene therapy for autosomal recessive deafness have failed to fully restore hearing. The partial restoration may be due to incomplete repair of the transmitters or central compensatory mechanisms, an area where neuroscience lags behind neurotechnology. However, neurotech is limited by neuroscience. He also outlined essential rules for developing neuroproducts: they must not cause harm, they should be sufficiently good and effective, and they must be sustainable for the businesses creating them. Fan-Gang emphasised the importance of transitioning from basic to translational research to ultimately help people.

Fang-Gang Zeng presenting his talk about cochlear implants for people with hearing impairment.

Selected short talks:

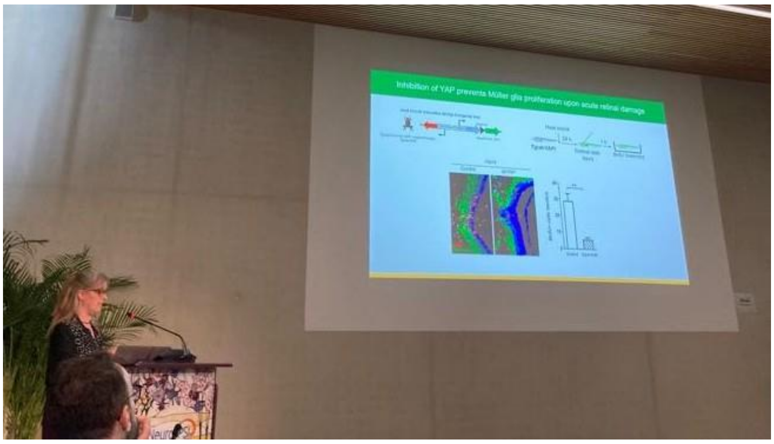
Serge Picaud, research director at the Paris Vision Institute, and his team are deeply engaged in developing potential solutions for visual restoration. Traditional brain-machine interfaces rely mainly on multiple electrode arrays. However, optogenetics has revolutionised the ability to control neuronal activity through the expression of opsins. Despite this, its application to larger brains remains limited due to light scattering in tissues. To address this limitation, Picaud's team is exploring sonogenetics, an approach that uses ultrasonic waves to activate neurons by expressing mechanosensitive proteins in them. By using a mechanosensitive ion channel called MscL, the team found that cortical neurons in rodents can be activated in vivo with high spatiotemporal resolution and low-intensity ultrasound. Based on these findings, they proposed developing an integrated sonogenetic strategy for the remote activation and inhibition of neural networks using ultrasound waves in large primate brains. This contactless technology will also help avoid fibrotic reactions in the brain, which can cause damage. On the other hand, **Thomas Deneux** at NeuroPSI and founder of Learning Robots, presented pedagogical innovations through understanding our brain and artificial intelligence. Numerous works on AI were inspired by neuroscience but in their work, they used AI to teach us something about the brain. To be specific, they used AI as a mirror to teach cognition. In their work, they have found that as early as 8 years old, pupils can understand AI and it can help them to change their metacognitive beliefs.

Session 4: Cellular and molecular restoration strategies

Muriel Perron
NeuroPSI, France

"Retinal regeneration: the Xenopus and the mouse perspectives"

Muriel Perron, head of the "Stem Cells and Neurogenesis in the Retina" team at NeuroPSI, gave an interesting talk about the use of endogenous stem cell therapy to regenerate lost or damaged photoreceptors. Her team works with both Xenopus (a highly regenerative species) and mouse (a poorly regenerative species) models to identify the mechanisms that enhance or restrict the proliferation of stem-like retinal Müller cells. She highlighted that regenerative capacity differs not only between species but also within an individual at different stages of life. She demonstrated that during Xenopus development, there is an early "refractory" period with minimal regeneration and a later "permissive" stage with strong regenerative ability. These stages may result from differences in levels of inflammation. Testing this hypothesis in mice, she found that inflammation enhances Müller cell proliferation, but inhibits their neuronal differentiation. She suggested that modulation of the neuroinflammatory environment could be the key to awakening regeneration in mammals and restoring vision in human retinopathies.



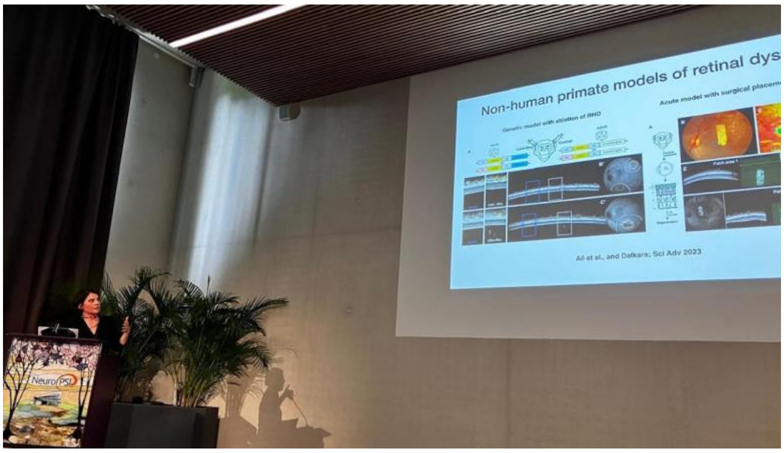
Muriel Perron presenting her work on the role of inflammation on retinal regeneration in two animal models: Xenopus and mouse.

Deniz Dalkara
The Vision Institute in Paris, France

"Disease state dependent gene therapy for inherited retinal degenerations"

Another approach to restoring vision for inherited retinal degeneration is gene therapy. Deniz Dalkara delivered an elaborate talk on using Adeno-Associated Viruses (AAVs) to introduce a functional copy of a gene into the eyes of patients. However, she quickly encountered a challenge: the AAV only incorporated into cells near the site of injection.

To overcome this, her team generated numerous AAV variants and tested their ability to reach the photoreceptors. Through directed evolution, they identified an AAV2 variant that worked perfectly in mice. The problem arose when testing it on non-human primates; it did not have the same effect. The issue was that the inner limiting membrane (ILM) in macaques is much thicker, acting as a barrier. When asked about the functional significance of the ILM and the possibility of removing it, Dalkara explained that the ILM plays a crucial role during retinal development, and efforts to remove it triggered a detrimental immune response. New studies have been launched to overcome this difficulty.

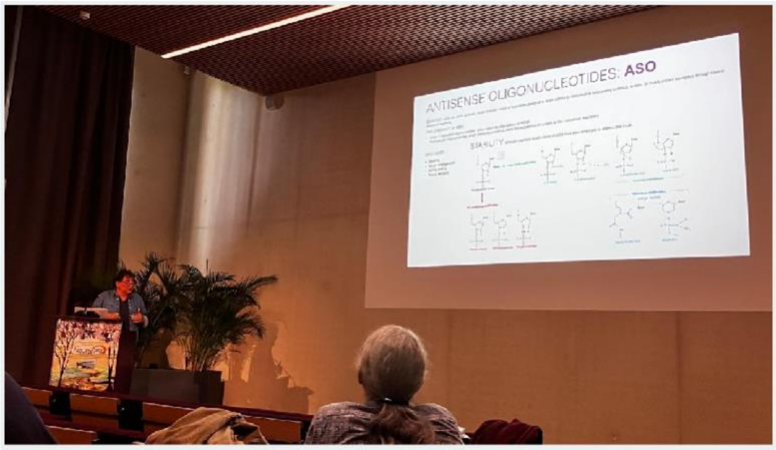


Deniz Dalkara showcasing her research about gene therapies for retinal diseases.

Luis Garcia
UVSQ, INSERM, France

"AVANCE 1: A novel tcDNA-based antisense oligonucleotide for dystrophin rescue in DMD patients eligible for exon-51 skipping"

Duchenne Muscular Dystrophy (DMD) is a severe form of muscle degeneration with a life expectancy of less than 30 years. It results from a mutation in the dystrophin gene, leading to a non-functional protein. A milder form of the disease, known as Becker Muscular Dystrophy (BMD), also exists. Luis Garcia and his team have designed antisense oligonucleotides for exon skipping that could rescue dystrophin production in DMD patients. He mentioned an ongoing clinical trial with SQY51, an antisense oligonucleotide designed to hybridise to a specific site on the transcribed pre-mRNA of the DMD gene. This process discards certain elements of the mutated gene during mRNA maturation (exon skipping) to restore the production of a functional truncated dystrophin. SQY51 uses unnatural nucleotides from the "tricyclo-DNA" family, which have the advantage of being very stable and hybridising more efficiently with their RNA targets than natural counterparts. He also presented information about the biotechnological company SQY Therapeutics, which emerged from an initiative by the parents of children affected by DMD, in collaboration with scientists. Their goal is to establish R&D programs for clinical purposes for genetic diseases and promote new therapeutic solutions for very disabling illnesses for which current care options remain unsatisfactory.



Luis Garcia presenting his work on the use of antisense oligonucleotides for the treatment of DMD

With this, we concluded the second annual NeuroPSI-Chen Institute Joint Conference. The event was a tremendous success, exploring relevant and timely topics on neuroengineering at the interface between electronics, robotics, and cellular biology. The talks were highly intriguing, and the poster sessions provided an interactive element attracting a significant audience eager to engage with students and young researchers from different corners of the world. Attendees left with a sense of interest to explore more in order to address issues on repairing sensorimotor and mental illnesses.

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This meeting report was written by Den Whilrex Garcia, Violeta Hernandez-Puente, and Demi van Westendorp. They wrote this meeting Report as part of the Tianqiao and Chrissy Chen Institute Science Writers Fellowship which aims to extend the conversation. Beyond the meeting with the hopes of sparking new ideas and collaborations.