II International Conference on Pharmacology & Gene Therapy for Tinnitus

Virtual Event | 2 October 2025 | 1:45 PM – 5:30 PM UK time (BST)

Abstracts Book

Welcome

I am delighted to welcome you to the second edition of the International Conference on Pharmacology & Gene Therapy for Tinnitus, a virtual gathering hosted from the United Kingdom. This focused half-day event brings together world-leading researchers and emerging voices in the fields of auditory neuroscience, pharmacology, genetics, and translational therapy. This is an opportunity to reflect on why our search for new solutions matters. Tinnitus research has advanced significantly, yet the underlying mechanisms remain partly hidden and a cure is still out of reach. While many manage their tinnitus with CBT or sound therapies, others live with severe, life-changing symptoms. In this opening session, I will highlight the moral and scientific imperative to connect fragmented findings, align biomarkers with therapeutic targets, and inspire collective action toward treatments that can reduce suffering.

At 2:00 PM, Professor Marlies Knipper will discuss objective biomarkers that may reveal the neural drivers of tinnitus and hyperacusis, guiding drug discovery and diagnostics. A 10-minute Q&A will follow each presentation throughout the event. At 2:30 PM, a trio of student presenters—Marlon Deutscher, Lea Müller, and Rodrigo Andrés Donoso San Martín present OPM-MEG imaging research that maps tinnitus-related brain activity with exceptional precision, offering new tools to measure treatment effects. At 3:00 PM, Dr Kelly Jahn shares patient insights on pain hyperacusis, highlighting unmet needs and guiding future interventions. At 3:30 PM, Dr Arnaud Norena discusses how noise-induced hearing loss disrupts GABAergic inhibition and may drive central hyperactivity. At 4:00 PM, Dr Wei Sun presents two models of hyperacusis, central gain and impaired sensory gating, with relevance for ASD. At 4:30 PM, Professor Thanos Tzounopoulos outlines pharmacotherapy development targeting KCNQ potassium channels. Finally, at 5:00 PM, Professor Richard Salvi presents findings from Fragile X models showing that mGlu5 receptor antagonists may normalise loudness perception, offering translational promise for ASD-related hyperacusis. Q&A concludes the programme. Together, these sessions chart a path from mechanism to medicine, reflecting our shared goal: transforming scientific insight into effective pharmacological and gene therapy interventions that bring relief to those most in need.

Hashir Aazh
Organizer

Welcome and Introduction (1:45 – 2:00 PM)

Hashir Aazh
Hashir International Institute, London, UK

Tinnitus research is advancing rapidly, yet its exact mechanisms remain elusive and finding a cure continues to be a challenge. Most people manage their tinnitus with therapies such as CBT and sound-based interventions, but a significant group still struggles with severe, persistent symptoms. This webinar opens by asking why we should continue striving for a cure despite these challenges. We now have an expanding knowledge base from functional biomarkers to genetic insights that can help us identify druggable targets and evaluate treatment success with greater precision. Today's programme brings together world-leading experts to explore neural mechanisms, genetic contributions, pharmacological models and outcome measures that will shape the next generation of tinnitus therapies. By uniting scientific evidence with a shared commitment to reducing human suffering, we aim to turn fragmented knowledge into coordinated progress toward safe and effective pharmacological and gene therapy interventions.

Need of Objective Functional Biomarkers to Find Druggable Targets for the Treatment of Tinnitus With or Without Hyperacusis (2:00-2:20 PM)

Marlies Knipper & Lukas Rüttiger
University of Tübingen, Department of Otolaryngology Head and Neck Surgery, Hearing Cognition and Tinnitus, Molecular Physiology of Hearing, Tübingen, Germany

An ongoing controversy whether tinnitus is linked with central neural gain, hampers efficient therapies for this burdensome disease. Based on numerous studies performed in tinnitus animal models and people affected by tinnitus, there is an agreement that tinnitus may be linked to hyperexcitability and elevated spontaneous activity in the brain, which unlikely result from hearing loss per se. As causal contributing factor a majority of tinnitus studies link tinnitus with deafferentation of cochlear inner hair cells. These studies to explain tinnitus in various hypothetical models e.g. dysrhythmia (TCD), neural gain theory, or e.g. synchronization by loss of inhibition (SLIM). We are trying to provide evidence from clinical trials that support previous discussed concepts of the origin of central hyperexcitability and the neural correlate of tinnitus. Based on this, we want to develop concepts for possible druggable targets and needs to use objective diagnostic tools for tinnitus validation.

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New Potential Insights in Druggable Tinnitus Targets from Cortical Activity Traits with OPM Imaging (2:30-2:50 PM)

Rodrigo Donoso-San Martín[1,2], Lea Müller1, Marlon-Sean Deutscher[1], Stephan M. Wolpert[2],Stefan Fink[1], Paul H. Délano[2], Christoph Braun[3], Lukas Rüttiger[1], Marlies Knipper[1]
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Despite high medical costs (Tziridis et al., 2022) and increased risk of early onset of dementia (Cheng Y-F et al., 2021),

a causal tinnitus therapy is still pending. Based on numerous studies performed in tinnitus animal models and tinnitus subjects, there is an agreement that tinnitus may be linked to central hyperexcitability and elevated spontaneous activity in the brain, that unlikely result from hearing loss by itself (Rüttiger et al., 2013, Wertz et al., 2024) Hypothesizing disease-specific deficits in temporal intracortical network function in auditory circuits in tinnitus which origin in peripheral auditory systems, we here choose objective tools for diagnosis. This study included controls and tinnitus subjects phenotyped by questionnaires to exclude the comorbidity of hyperacusis. Pure-Tone Audiometry and suprathreshold auditory brainstem responses were used next to specify auditory processing changes in tinnitus. Spontaneous and auditory evoked magnetic field responses in control and tinnitus subjects were measured with high-temporal resolution using a 64 channel optically pumped magnetometer (OPM-MEG) device that is implemented at the third floor of the ENT clinic in Tübingen. We present first findings for differences of spontaneous and evoked AEF in distinct slow and fast brain oscillation frequencies. The findings supports that tinnitus correlate, which we have postulated for a long time. It explains and complements a number of existing hypothesis on tinnitus. With our new objective diagnostic procedure, pharmacological, cognitive-associated and medical device-based therapeutic approaches for tinnitus and hyperacusis can now be ideally validated.

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Efficacy of Pharmacological Interventions for Pain Hyperacusis: Preliminary Insights from the Patient Perspective (3:00-3:20 PM)

Kelly N. Jahn
The University of Texas at Dallas, USA

Pain hyperacusis, also known as noxacusis, is a disorder that causes physical pain in response to sounds that do not bother most people. More than 90% of individuals afflicted with pain hyperacusis also experience tinnitus, indicating that the two conditions are highly co-morbid. Despite the debilitating nature of pain hyperacusis, we do not know how everyday sounds could cause excruciating pain, and we do not have widely effective treatments for the disorder. To guide future work on the neural mechanisms of pain hyperacusis and effective therapies, we interviewed 32 adults with debilitating sound-induced pain to better understand their experiences with available treatment options. The participants indicated that they have tried numerous pharmaceutical and non-pharmaceutical interventions to manage their pain. The qualitative data suggest that these therapies have led to varying degrees of pain relief that vary from person-to-person. In this presentation, we will discuss the preliminary insights that these patients provided and next steps for investigating potential interventions for pain hyperacusis.

Noise-Induced Hearing Loss Alters Potassium-Chloride Cotransporter KCC2 and GABA Inhibition in the Auditory Centres (3:30-3:50 PM)

Arnaud Norena
Université Aix-Marseille, France

Homeostatic plasticity, the ability of neurons to maintain their averaged activity constant around a set point value, is thought to account for the central hyperactivity after hearing loss. Tinnitus and hyperacusis may

be a by-product of this mechanism. We investigated the putative role of GABAergic neurotransmission in this mechanism after a noise-induced hearing loss. The effect of GABAergic inhibition is linked to the normal functioning of K + – Cl– co-transporter isoform 2 (KCC2) which maintains a low intracellular concentration of chloride. The expression of membrane KCC2 were investigated before and after noise trauma in the cochlear nucleus and in the inferior colliculus. Moreover, the effect of gabazine (GBZ), a GABA antagonist, was also studied on the neural activity in IC. We show that KCC2 is downregulated in the centres. As expected, GBZ application in the IC of control animals resulted in an increase of spontaneous and stimulus-evoked activity. In the noise exposed animals, on the other hand, GBZ application decreased the stimulus evoked-activity in IC neurons. The functional implications of these central changes will be discussed.

Central Gain and Neural Adaptation Model of Hyperacusis (4:00-4:20 PM)

Wei Sun & Fei Xu
Department of Communicative Disorders and Sciences, State University of New York at Buffalo, USA

Hyperacusis is a devastating disorder that affects people's lives. The symptom is commonly reported in people after noise exposure or in children with neurological disorders, including Williams syndrome, FoxG1 syndrome and autism spectrum disorders (ASD). Increased neural activities in the central auditory system (CAS) to compensate for the hearing loss, named "central gain", are thought to underlie the cause of hyperacusis. However, as most people who experience hearing loss do not develop hyperacusis, it is unclear whether the "central gain" represents a plasticity change of the CAS to the hearing loss or the cause of hyperacusis.

In this study, we used two different animal models of hyperacusis, i.e., the noise exposure model and the FoxG1 gene mutation model, to study the neurological model of hyperacusis. CBA mice, wild-type mice, and FoxG1 gene mutation mice (G216S) were used in the experiment. Low-level noise exposure (83 dB SPL, 2 weeks, 12 hrs/per day) was used to induce hyperacusis in the WT mice. FoxG1 mutant mice were used as genetic model of hyperacusis. Acoustical startle responses (ASR) were used to evaluate sound sensitivity, and gap-induced prepulse inhibition (gap-PPI) was used to evaluate sensory gating. The auditory cortex (AC) response was measured in the control, noise-exposed, and FoxG1 mutant mice. Auditory brainstem response (ABR) was used to evaluate peripheral hearing loss.

ABR results showed no significant hearing loss was induced in the noise group or FoxG1 gene mutant group. Enhanced ASR and increased gap-PPI were recorded in the noise model. A significant enhancement of AC onset response was recorded in noise-induced mice, an indication of "central gain". FoxG1 mice showed no significant enhancement of the ASR. However, the ASR showed a lack of habituation for repetitive acoustic stimuli. These mice also showed a lack of gap-PPI suggesting impaired sensory gating caused by FoxG1 gene mutation. The AC recording shows no signs of enhanced response, but longer post-stimuli responses.

Our findings highlight two distinct models of hyperacusis: noise exposure-induced central gain and a neural adaptation model in FoxG1 mutants, consistent with reports in ASD patients. Our study suggests that (1) central gain is not a result of a cortical compensatory response to peripheral lesions, but rather an enhanced synaptic processing; and (2) a lack of sound habituation due to cortical immaturity may contribute to altered sound tolerance and loudness perception, potentially explaining hyperacusis in children with ASD.

Efforts Towards Developing a Pharmacotherapy for Tinnitus and Hyperacusis and the Role of KCNQ Potassium Channels (4:30-4:50 PM)

Thanos Tzounopoulos
University of Pittsburgh, USA

In my talk, I will discuss the role of KCNQ potassium channels on tinnitus and hyperacusis. Moreover, I will describe our drug development efforts towards developing a pharmacotherapy.

Hyperacusis in Fragile X Model of Autism: Dose-Dependent Drug Treatment (5:00-5:20 PM)

Richard Salvi
University of Central Florida, USA

Fragile X (FX) syndrome is one of the leading genetic causes of (ASD). FX syndrome is associated with a CGG expansion near the Fmr1 gene resulting in FMRP protein deficiency. To determine if male Fmr1 knockout (KO) rats have hyperacusis, we assessed loudness growth functions by measuring behavioural reaction times (RT) to tone bursts or noise bursts over a range of sound intensities (RT-I). Fmr1 KO and normal wild type (WT) rats had similar behavioural thresholds in quiet. However, at suprathreshold intensities, Fmr1 KO rats had significantly shorter RTs, evidence that Fmr1 KO rats suffer from hyperacusis. To test for abnormal temporal integration of loudness, we measured RT-I functions with 50, 100 and 300 ms tone bursts. RTs decreased with increasing duration in WT rats, evidence of temporal integration of loudness. In Fmr1 KO rats, RTs were shorter than in WT rats and their RTs were unaffected by duration, evidence of abnormal temporal integration of loudness. To test for spectral integration of loudness, RT-I functions were measured with tone or noise bursts with signal bandwidths from 1 Hz to 2 octaves wide. In WT rats, RTs remained constant for signal bandwidths up to 1/3 octave. In contrast, RTs decreased for bandwidths greater than 1 Hz in Fmr1 KO rats, evidence of abnormal spectral integration of loudness. The MTEP-mGlu5 receptor has been implicated in ASD. To investigate its role in hyperacusis, RT-I functions were measured in Fmr1 KO and WT rats before and after treatment with an MTEP mGlu5 receptor antagonist. The MTEP mGlu5 receptor antagonist had no effect on RTs in WT rats; however, RTs in Fmr1 KO rats increased to normal RT values as drug dose increased. These results suggest that MTEP-mGlu5 antagonists might be clinically effective at suppressing loudness hyperacusis in individuals with ASD.