

Pharma Workgroup

A. People:

Project Leader:

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Principal Investigators: Clinical Trials

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Principal Investigators: Animal Studies

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B. Specific Aim:

The primary aim of the workgroup is to find a compound/s to alleviate or abolish subjective tinnitus.

Rationale:

- ***There is no reason a priori to believe that neuronal activity-driven changes underlying tinnitus cannot be pharmacologically targeted.***
- ***A drug that produces even a small therapeutic effect can have a huge impact. However, disappearance (extinction) of tinnitus should be the ultimate goal.***

The second aim of the workgroup is to have first hand information concerning pharmacological treatment of tinnitus.

C. Rational and Background:

An estimate of over 20 million people in Western Europe and the USA currently seek medical advice for their tinnitus. Over 4 million prescriptions are written each year for tinnitus relief but these are all for off-label drugs from a wide variety of therapeutic classes and most are associated with considerable side effects. Despite the significant unmet clinical need for a safe and effective drug targeting tinnitus relief, there is currently not a single FDA-approved drug on the market for tinnitus as its primary indication. The global demand for therapeutic treatments is increasing dramatically with industrialization and longer lifespan. In developed countries the appetite for leisure noise among the

young is expected to have a substantial, deleterious impact on hearing loss and a significant increment in the incidence of tinnitus in older generations in the future.

It has long been understood by pharmaceutical companies that there is a large market for a drug indicated for tinnitus relief. Evidence for this exists in the scores of patents that have been filed world wide on potential drugs that may offer relief. Furthermore, tinnitus can be found attached to long lists of indications in many more patents filed on molecules aimed at a range of diverse therapeutic classes. A large number of pharmacological agents have been used to treat individuals with tinnitus: anticonvulsants, anxiolytics, antidepressants, NMDA-antagonists, cholinergic antagonists, antihistamines, to name a few. None have proven sufficiently effective in randomized controlled clinical trials to allow them to be marketed specifically for tinnitus.

Tinnitus is a symptom that is associated with virtually all diseases and disorders affecting the auditory system and can arise from a lesion in any part of the auditory pathway. The site of origin of the sound percept may be in the central auditory circuitry even if the initial lesion is in the periphery of the auditory system. Some causes, such as noise-induced hearing loss, that trigger tinnitus are well known. Although the mechanisms of the production of tinnitus are far from being fully understood, there is growing evidence that there is a correlate of tinnitus with changes in neuronal activity in the dorsal cochlear nucleus, inferior colliculus, thalamus and/or auditory cortex. Neuronal excitability can be modulated by different neurotransmitters, neuromodulators and voltage-gated channel acting compounds, so **there is no reason to believe that activity-driven changes underlying tinnitus cannot be pharmacologically targeted.**

In some individuals, tinnitus causes irritability, agitation, stress, depression and insomnia (therefore affecting their quality of life) and for some it interferes with normal life. **Therefore, a drug that produces even a small effect can have a huge impact. However, disappearance (extinction) of tinnitus should be the ultimate goal.**

D. Strategies:

1. Identify compounds.

Among drugs which are already on the market (approved for other conditions) the workgroup aims to identify those which have a high chance to have an effect on tinnitus. Even if we are not focussing on new compounds to commercialize we are open to the possibility of joint projects with pharma companies for new non-marketed promising compounds.

2. Animal studies.

In general drug development strategies in pharma companies are based on pre-clinical studies done on *in vitro* assays and/or in animals. Pursuing with a compound which is not promising at this step is too risky and is not done in a pharmaceutical setting. Which possibilities for preclinical testing are available in tinnitus?

- Some neural substrates for tinnitus, which could eventually be used to monitor drug effects. These include changes in neuronal activity at the level of the cochlear nucleus, inferior colliculus, thalamus and auditory cortex. However, it is not clear at present that one can consider any of these neuroendophenotypes as a fingerprint of tinnitus in order to assess drug effects.
- A series of behavioral animal models.

The use of animal models to study human disease has been well recognized for centuries. Significant understanding of fundamental mechanisms of disease and the development of effective treatments has often depended on the use of animal models. For example, key developments in understanding and treating pain were derived from animal research. Similarly, an animal model may be able to provide answers to fundamental questions about tinnitus mechanisms and treatments. Animal research designs can directly control many sources of variance, which contribute to the heterogeneity of tinnitus (eg, age, exposure to acoustic trauma or ototoxic agents, and genotype). Animal subjects permit the ethical use of tinnitus induction procedures and the use of invasive procedures to investigate the pathophysiology of tinnitus. An animal model can be used to study the histologic, neurochemical, and systematic changes within the peripheral and central auditory system that are directly responsible for the perception of tinnitus. It may be that only through use of an animal model will one be able to test hypotheses of tinnitus generation deriving from the many theories advanced to explain tinnitus. Moreover, and in relation to the pharma workgroup, validated animal models are the

only way to screen drugs in a semi-high throughput and reproducible fashion. In addition, they are the only way to test drugs that are still in the R&D stage at pharma companies and not yet approved for the use in humans.

Although it may be obvious that fundamental questions about tinnitus may be answered best using well-designed animal studies, it may not be as obvious that the prerequisite for such studies is reasonable and possible (e.g., that animals can experience tinnitus, and that the experience can be objectively measured). If tinnitus results from pathologic changes in the basic mechanisms of sound transduction and neural processing of acoustic information, then there is no a priori reason to conclude that an animal cannot experience this sensation. Small mammals, such as cats and rodents (mouse, hamster, guinea pig, chinchilla, and rat), are routinely used as subjects in studies of auditory processing. Auditory processing from the level of the hair cell mechanics within the cochlea to plasticity within the auditory cortex has been studied. Most of the basic understanding of the organization and pharmacology of central auditory systems is based on animal work. Information from these studies is routinely extrapolated to human auditory function.

Over the last fifteen years, various animal models of tinnitus have been developed and salicylate, quinine, and noise induced tinnitus have been studied in rodents. The limitations of the models have not been related to tinnitus detection but rather the long term study of tinnitus, extinction of the tinnitus assay, long training times, low throughput, and the use of group rather than individual data. These factors have made the study of tinnitus using animal subjects very labor intensive and required dedicated laboratory equipment and personnel not readily available in many basic auditory research labs. Over the last four years the Schedule Induced Polydipsia Avoidance Conditioning (SIP-AC) and the development of the Gap Prepulse Inhibition of the Acoustic Startle (GPIAS) adapted for tinnitus, have resulted in a dramatic reduction in training times, are suitable for long term tinnitus measurement, produce detailed individual data, and are resistant to extinction. Research laboratories in Europe and the United States have already begun using these models to look at potential pharmacological treatments of tinnitus. Experiments at the University at Buffalo have cross validated both of these models for transient and permanent tinnitus. This cross validation is important because it supports the use of the GPIAS as a fast throughput screening device for drugs that could reduce or suppress tinnitus. Additionally, GPIAS requires no overt training thus reducing inter-laboratory and inter-experiment variability. Currently, the GPIAS is the most cost- and labor- efficient animal model under which to screen tinnitus treatment. Further validation of results of GPIAS could be confirmed using SIP-AC as a secondary assay to determine treatment efficacy. It is important to note that both of these models have built in control conditions to differentiate between the effects of hearing loss from the presence of tinnitus. The results obtained over the various animal models of tinnitus have shown results consistent with the perception of a phantom sound.

The animal data indicate that the sensation of tinnitus, the perception of a sound in the ear or head, or even outside the head, that does not derive from acoustic energy, is an aspect of tinnitus that does not require cognitive or language function to be present. In other words, because it is likely that tinnitus arises from basic pathologic changes at one or more levels in the auditory system, tinnitus should be capable of being induced in most animals reliably. At the level of sensation, tinnitus is a primitive percept. This is in contrast to the emotional or limbic associations that occur in many, but not all, people with tinnitus. The emotional distress associated with tinnitus, an unavoidable, persistently intrusive sound, is a comorbidity that may be unique to humans. This emotional aspect of tinnitus occurs as a response to an evaluation of the auditory sensation. Whether animals experience emotional distress in response to tinnitus is unknown, and therefore this is an unavoidable caveat of behavioral animal models. However, predictors of which people will be distressed by tinnitus and which will respond without emotion are likewise unknown. The advantage of the animal models is that it allows the studies to focus primarily on reducing the perception of tinnitus. This is an important prerequisite to studying tinnitus in humans and the complex interaction between the sensation of tinnitus and the resulting emotional response.

3. Studies in Humans: Systematic Clinical Observations.

Serendipity has served tinnitus badly and very little success has been provided by reports from patients or professionals concerning drugs that are licensed and used for other indications being useful in the treatment of tinnitus. It is surprising, considering the widespread occurrence of tinnitus and its incidence in older people who are more likely to require treatment for other conditions, that very few claims have been made that other drugs are effective in tinnitus. Whenever such reports have been made, the necessary trials of such substances have either been inadequately performed or not carried out at all. This has resulted in the promotion of various “therapies” throughout the world without

the existence of any adequate evidence for their effectiveness. This has involved both orthodox medicines and complementary therapies including food additives and herbal preparations. Discrepancies in the different findings are not difficult to explain. Tinnitus is notorious for being difficult to assess. A general tinnitus population will have patients with tinnitus as a result of many different underlying pathologies and the placebo response usually runs at around 30 to 40%. Furthermore, patient selection is of crucial importance; the results of a trial can hinge entirely on how the patients are selected.

Great care must be taken in conducting drug trials. Small, open or uncontrolled trials are of little value in the assessment of a drug's effectiveness. This probably applies more to tinnitus than to most other indications as the severity of tinnitus is difficult to assess and the placebo response is usually enormous. Open, uncontrolled trials, however, have certain advantages. Such testing by a physician in the clinic can be of considerable value in assessing doses, adverse responses, and the general problems that might arise in the running of a full double blind, placebo-controlled trial. Moreover, they can give us some hint of promising drugs (that can then be taken into a controlled double blind study). However, claims about the effectiveness of an agent gathered from data collected in an open trial should be discarded or at least recognized as being possibly erroneous.

4. Pharma Connections

The TRI Pharma workgroup is interested in all forms of collaboration with the pharmaceutical industry.

5. Collecting Ideas

The TRI pharma workgroup is highly interested in reports from tinnitus patients about their experience with drugs they might have taken for other conditions.