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Noise-induced hearing loss: Translating risk from animal models to real-world environments

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Noise-induced hearing loss (NIHL) is a common injury for service members and civilians. Effective prevention of NIHL with drug agents would reduce the prevalence of NIHL. There are a host of challenges in translation of investigational new drug agents from animals into human clinical testing, however. Initial articles in this special issue describe common pre-clinical (animal) testing paradigms used to assess potential otoprotective drug agents and design-related factors that impact translation of promising agents into human clinical trials. Additional articles describe populations in which NIHL has a high incidence and factors that affect individual vulnerability. While otoprotective drugs will ultimately be developed for use by specific noise-exposed populations, there has been little effort to develop pre-clinical (animal) models that accurately model exposure hazards across diverse human populations. To facilitate advances in the translational framework for NIHL otoprotection in pre-clinical and clinical testing, the overarching goals of the current series are to (1) review the animal models that have been used, highlighting the relevance to the human populations of interest, (2) provide insight into the populations for whom pharmaceutical interventions might, or might not, be appropriate, and (3) highlight the factors that drive the significant individual variability observed in humans. https://doi.org/10.1121/1.5133385

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I. NIHL

Noise-induced hearing loss (NIHL) is one of the most common injuries for service members and it is also one of the most common disabilities for veterans (Yankaskas, 2013; Gordon *et al.*, 2017; Nelson *et al.*, 2017; Swan *et al.*, 2017). NIHL carries a significant financial cost with respect to treatment, which is often in the form of auditory rehabilitation (generally via hearing aids), and has a negative impact on the quality of life for affected individuals (Yankaskas, 2013; Yankaskas and Komrower, 2019). NIHL is also one of the most prevalent occupational injuries (Tak *et al.*, 2009; Kerns *et al.*, 2018), and there have been various efforts to reduce NIHL over many years (Kerr *et al.*, 2017). Worldwide, some 16% of disabling hearing loss [defined using the World Health Organization (WHO) criteria of 41 dB hearing level or poorer pure-tone average threshold at 1, 2, 3, and 4 kHz] has been suggested to be attributable to occupational noise exposure (Nelson *et al.*, 2005; see also the recent review by Graydon *et al.*, 2019). There is also concern about adolescent and young adult populations based on a recent report by the WHO, which indicated that some 1.1×10^9 young people worldwide may be at risk for NIHL based on both personal audio system use and exposure to amplified music in bars, clubs, and concerts (World Health Organization, 2015). While much of the data assessing potential relationships between non-occupational noise exposure and hearing loss have been of low quality (as per the systematic review by Sliwinska-Kowalska and Zaborowski, 2017), the number of individuals that may be at risk for NIHL as a consequence of recreational and other non-occupational exposures highlights the compelling need for additional research.

The total economic cost of hearing loss, including NIHL, is more than $\$750 \times 10^9$ annually worldwide (Neitzel *et al.*, 2017). Thus, it is promising that recent data suggest those born in more recent generations have better hearing than those born in earlier generations (Zhan *et al.*, 2010). It is also promising that there has been an overall decrease in the prevalence of hearing loss in adults when cross-sectional data collected in different years are compared (Hoffman *et al.*, 2017). However, despite these positive trends, nearly 25% of the adults sampled in a nationally representative cohort had notched audiometric configurations consistent with noise-induced injury (using a definition of a notch that includes a 15 dB deficit at 3, 4, or 6 kHz; see Carroll *et al.*, 2017). The large number of affected individuals across noise-exposed populations has therefore driven significant interest in translation of therapeutics from animal models to human clinical trials (Le *et al.*, 2017; Wang and Puel, 2018; Kujawa and Liberman, 2019; Le Prell, 2019), as well as interest in whether there may be differences in therapeutic benefit associated with different types of noise injury (Wada *et al.*, 2017).

Clinical trials in humans have explored prevention of temporary threshold shift (TTS) using several different clinical trial models with mixed results across drugs and

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paradigms (Attias *et al.*, 2004; Quaranta *et al.*, 2004; Kramer *et al.*, 2006; Quaranta *et al.*, 2012; Le Prell *et al.*, 2016; Kil *et al.*, 2017). Fewer efforts have been made to assess prevention of permanent threshold shift (PTS) in human clinical trials (Attias *et al.*, 1994; Kopke *et al.*, 2015; Campbell, 2016). In parallel to efforts targeting improved situational awareness using Tactical Communication and Protective System devices (Clasing and Casali, 2014; Casali and Robinette, 2015), the development of drugs that reduce or prevent NIHL has also emerged as being of significant interest to the U.S. Department of Defense (DoD). The loss of situational awareness due to the sound attenuation provided by hearing protection devices and/or the hearing loss induced by noise exposure significantly impacts fitness for duty (Tufts *et al.*, 2009; Casto and Cho, 2012; Bevis *et al.*, 2014; Semeraro *et al.*, 2015; Sheffield *et al.*, 2017).

II. INTRODUCTION TO THE HEARING CENTER OF EXCELLENCE

Based on the prevalence, impact, and cost of NIHL, the DoD Hearing Center of Excellence (HCE) was legislated by Congress in the 2009 National Defense Authorization Act. The HCE is focused on the prevention, diagnosis, mitigation, treatment, and rehabilitation of hearing loss and auditory injury, and it includes partnerships with the Department of Veterans Affairs (VA), institutions of higher education, and other public and private organizations. The mission of the DoD HCE is to enhance operational performance, medical readiness, and quality of life through collaborative leadership and advocacy for hearing and balance health. Toward this end, the HCE has sponsored several open-access supplemental journal issues to promote knowledge and research in the overall area of Pharmaceutical Interventions for Hearing Loss (PIHL), managed by committees established under the umbrella of the DoD HCE PIHL Group.

III. PREVIOUS PIHL PUBLICATIONS

The first HCE-sponsored series of articles [Otology and Neurotology, Vol. 37(8), 2016] included seven articles that reviewed and discussed best practices for human research into NIHL and its prevention (for an introduction to the special issue, see Hammill and Packer, 2016). Contributions to this initial series discussed the pathological basis of TTS and PTS (Ryan *et al.*, 2016), the criteria for identification and monitoring of significant noise-induced threshold shift (Campbell *et al.*, 2016), and clinical metrics that could be considered for use in clinical trials including otoacoustic emissions (Konrad-Martin *et al.*, 2016), speech-in-noise and auditory evoked potential testing (Le Prell and Brungart, 2016), tinnitus surveys (Henry, 2016), and the use of biomarkers as an adjunctive measure in clinical trials (Haase and Prasad, 2016). In addition, this series included a review of the genetic basis of NIHL, organized within cellular stress response pathways such as heat shock response, free radical generation, and immune response (Clifford *et al.*, 2016). Taken together, these articles provided guidance on best practice procedures that should be included in all investigations of NIHL, and a review of the current level of evidence regarding other test protocols that could be considered for use in human clinical investigations.

The second HCE-sponsored series of articles (Hearing Research, Vol. 349, 2018) included 23 articles in two topic areas: impact of noise in the military and biological mechanisms of NIHL (for an introduction to the special issue, see Yankaskas *et al.*, 2017b). The issues of impulsive (Davis and Clavier, 2017) and long-term (Davis, 2017) noise were briefly defined, and noise-induced injury was described (Caspary and Llano, 2017; Chen *et al.*, 2017; Kurabi *et al.*, 2017). The problem and prevalence of hearing loss in veterans was reviewed in detail (Gordon *et al.*, 2017; Nelson *et al.*, 2017; Swan *et al.*, 2017). One of the major issues for military populations is communication in noise, and multiple contributions discussed this issue from a variety of perspectives (Bressler *et al.*, 2017; Brungart *et al.*, 2017; Keller *et al.*, 2017; Le Prell and Clavier, 2017; Manning *et al.*, 2017). The potential effects and issues related to cochlear synaptopathy were a topic of significant interest, with reviews and commentary contributed by several teams (Hickox *et al.*, 2017; Kobel *et al.*, 2017; Liberman and Kujawa, 2017; Lobarinas *et al.*, 2017). The pathway through the Food and Drug Administration review process was described (Hammill, 2017), and the concept of drug discovery using spiral ganglion cell cultures for screening purposes was introduced (Whitlon, 2017). Other topics discussed in this special issue included the importance of engineering controls (Yankaskas *et al.*, 2017a), advances in dosimetry (Smalt *et al.*, 2017), modeling of the noise-damaged auditory system (De Paolis *et al.*, 2017), and an introduction to hair cell regeneration (Zheng and Zuo, 2017). As introduced below (see Sec. IV), the current special issue expands on these earlier efforts providing a focused discussion of additional populations impacted by noise, the factors that result in individual variation in vulnerability to NIHL, and the animal models that have been used in pre-clinical drug development efforts.

For completeness, it should be noted that the HCE also sponsors work in the area of drug-induced hearing loss, and two additional HCE-sponsored series of articles have been published on this topic. The third HCE-sponsored series of publications (Frontiers in Cellular Neuroscience, Research Topic: Cellular Mechanisms of Ototoxicity, 2018) included 23 basic scientific articles and reviews addressing the cellular mechanisms of ototoxicity and its prevention (for an introduction to the special issue, see Steyger *et al.*, 2018). The fourth and most recent series of manuscripts sponsored by the HCE [International Journal of Audiology, Vol. 57(4), 2018] further reviewed and discussed ototoxicity in humans in a series of 11 review papers (for an introduction to the special issue, see Boudin-George *et al.*, 2018).

IV. INTRODUCTION TO THE SPECIAL ISSUE

The articles in the current special issue of the Journal of the Acoustical Society of America highlight populations in which NIHL is commonly detected, factors that influence individual variability, variation in study design used for the pre-clinical testing of potential otoprotective drug agents in animal models, and resulting challenges in the translation of drugs from animal model testing paradigms to human clinical trials. Otoprotective drugs will ultimately be developed for and targeted to specific populations and markets, but currently, there is only a limited understanding of who the at-risk populations are and what the most appropriate clinical trial paradigms will be, and the drug development pathway is often not clear to those working in this area (for a detailed review, see contribution by Cousins, 2019). The articles contained in this series of papers are organized to describe the animal models that have been used in pre-clinical drug development paradigms (Section 1), contrasted with selected real-world noise hazards and patterns of injury (Section 2), followed by explanations of variability sources (Section 3), so that the most appropriate test paradigms can be selected when a drug is initially developed for potential application.

Section 1. One of the overarching goals of this special issue was the development of a series of papers documenting and describing the various animal models that are routinely used to assess prevention of NIHL via investigational new drug agents. These models include the mouse (Ohlemiller, 2019), rat (Escabi *et al.*, 2019; Holt *et al.*, 2019), chinchilla (Trevino *et al.*, 2019; Radziwon *et al.*, 2019), and guinea pig (Naert *et al.*, 2019). Although non-human primates have not commonly been used in the assessment of otoprotective drug agents, there are compelling reasons to study auditory function and protection against noise injury in non-human primates (Burton *et al.*, 2019). Non-human primates are less vulnerable to NIHL than rodents, which has significant implications for hypotheses about the vulnerability of the human auditory system. Additional papers within this section discuss various laboratory-based exposure paradigms including impulse noise (Bielefeld *et al.*, 2019), octave band noise (Gittleman *et al.*, 2019), and blast exposure (Zhang, 2019). The organization of the manuscripts including discussion of different noise models used across different species is summarized in Table I.

Section 2. A second overarching goal of this special issue was the development of a series of papers documenting and describing various populations that are at risk for NIHL. Not only is discussion of real-world noise environments that are associated with increased incidence of NIHL critically important for identification of potential patient populations, it is vital for improving the real-world relevance of the animal models used during initial drug screening and development. Building on the previous HCE-sponsored publications describing the problem and prevalence of hearing loss in veterans (Gordon *et al.*, 2017; Nelson *et al.*, 2017; Swan *et al.*, 2017), the current series includes a detailed discussion of the relationships between noise exposure and tinnitus in service members and veterans (Bramhall *et al.*, 2019). Additional contributions describe the problem of noise in the military (Jokel *et al.*, 2019) as well as efforts within the DoD to address gaps in knowledge (Hecht *et al.*, 2019). The current series also reviews issues of hazardous firearm noise (Murphy and Xiang, 2019; Wall *et al.*, 2019). Finally, the series includes content regarding civilian populations, with exposure to other high level noise exposures resulting in

TABLE I. Organization of articles according to species and noise type.

	Impulsive Noise	Chronic Noise	Blast	Hidden Injury
Mouse	Ohlemiller (2019)	Clifford *et al*. (2019)		Ohlemiller (2019)
		Fontana *et al*. (2019)		
		Frye *et al*. (2019)		
		Gittleman *et al*. (2019)		
		Ohlemiller (2019)		
Rat	Bielefeld *et al*. (2019)	Escabi *et al*. (2019)	Escabi *et al*. (2019)	Escabi *et al*. (2019)
	Escabi *et al*. (2019)	Gittleman *et al*. (2019)	Holt *et al*. (2019)	Holt *et al*. (2019)
	Holt *et al*. (2019)	Holt *et al*. (2019)	Zhang (2019)	
Guinea Pig	Bielefeld *et al*. (2019)	Gittleman *et al*. (2019)	Bielefeld *et al*. (2019)	Naert *et al*. (2019)
	Naert *et al*. (2019)	Naert *et al*. (2019)	Zhang (2019)	
Chinchilla	Bielefeld *et al*. (2019)	Gittleman *et al*. (2019)	Trevino *et al*. (2019)	Trevino *et al*. (2019)
	Trevino *et al*. (2019)	Trevino *et al*. (2019)	Zhang (2019)	Radziwon *et al*. (2019)
	Radziwon *et al*. (2019)	Radziwon *et al*. (2019)		
Non-human Primate	Burton *et al*. (2019)	Burton *et al*. (2019)	Burton *et al*. (2019)	Burton *et al*. (2019)
Human	Deiters *et al*. (2019)	Berger and Dobie (2019)	Hecht *et al*. (2019)	Bramhall *et al*. (2019)
	Feder *et al*. (2019)	Cantley *et al*. (2019)	Jokel *et al*. (2019)	Cousins (2019)
	Hecht *et al*. (2019)	Clifford *et al*. (2019)		Kamerer *et al*. (2019)
	Jokel *et al*. (2019)	Feder *et al*. (2019)		
	Murphy and Xiang (2019)	Grinn and Le Prell (2019)		
	Wall *et al*. (2019)	Hecht *et al*. (2019)		
		Jokel *et al*. (2019)		
		Neitzel and Fligor (2019)		
		Roberts and Neitzel (2019)		
		Rosowski *et al*. (2019)		
		Spankovich and Le Prell (2019)		
		Themann and Masterson (2019)		
		Wartinger *et al*. (2019)		

acoustic trauma (Berger and Dobie, 2019), as well as civilian populations exposed to occupational noise (Themann and Masterson, 2019), music industry professionals exposed to loud music (Wartinger *et al.*, 2019), and adults (Neitzel and Fligor, 2019) and children (Roberts and Neitzel, 2019) exposed to recreational (leisure) noise exposure. The types of noise characteristic of the populations within each manuscript are broadly classified within Table I. Related discussions drawing from other real world populations are provided in contributions from Feder *et al.* (2019) and Kamerer *et al.* (2019). Understanding of the populations that are potentially at risk for noise injury is important both for the development of pre-clinical test paradigms that more accurately mimic the human exposure, as well as the identification and development of clinical trial protocols for human testing.

Section 3. The third and final overarching goal of this special issue was the development of a series of papers documenting and describing the various factors that influence individual vulnerability to noise injury. It has long been known that some individuals are more vulnerable than others, meaning they develop more NIHL despite common exposure histories. Some of these individual differences may be related to peripheral factors, such as the external and middle ear (Grinn and Le Prell, 2019; Rosowski *et al.*, 2019), and the strength of the acoustic reflex (Deiters *et al.*, 2019). Other contributing factors appear to include individual genetic variation (Clifford *et al.*, 2019), hormone signaling (Shuster *et al.*, 2019), inflammatory response (Frye *et al.*, 2019), nutritional status (Spankovich and Le Prell, 2019), and the time of day at which the exposure occurs (Fontana *et al.*, 2019). Additional data suggest that baseline hearing at the onset of exposure and the rate at which early changes in hearing are observed are associated with later NIHL progression (Cantley *et al.*, 2019). There has been virtually no effort to account for any of these factors in clinical trials to date. Many of the papers included in Section 3 provide broad reviews across species and noise injury models, but papers have been listed within Table I with as close a fit as possible.

V. SUMMARY

The articles included in the current series of papers expand the emphasis of previous work sponsored by the DoD HCE PIHL committees in new translational directions. These papers were specifically invited with the goal of furthering the development of otoprotective drug agents that will decrease the prevalence, impact, and cost of NIHL, not only for the DoD and the VA but also for industry and the general public. Authors invited to contribute manuscripts were specifically asked to consider the issues of drug development and/or clinical trial design, and the editors are grateful for the authors' outstanding efforts and contributions to this series. The final paper in this series provides comprehensive discussion of the overlapping themes across the special issue papers.

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