Come fly with me

Professor Martin Göpfert discusses his group's research into the cellular biology of hearing, and reveals why the common fruit fly may hold the key to a better understanding of the causes of human deafness

As an introduction, can you outline the aims of your current project?

Hearing impairment is the most common sensory deficit in humans. Various forms of hearing impairments have genetic causes, but many of the responsible genes remain hidden. One of the genetic model organisms which can be used to narrow down candidate deafness genes is *Drosophila*, more commonly known as the fruit fly. These insects communicate acoustically via courtship songs, using their antennae as ears to listen to each other. By analysing the genetic repertoire of the fly's auditory organ and by genetically dissecting its sensory function, we aim to identify candidate genes for deafness, and furthermore to characterise their roles in hearing.

Why is the hearing organ of the fruit fly your preferred model system? How closely correlated is the genetic repertoire of the fly's auditory receptor cells to those in human ears?

Drosophila genetics offers powerful tools for dissecting hearing, and the creature's antennal ears facilitate auditory function. Unlike those of humans, the ears of the fruit fly stick out of its head, resulting in a sound receiver that is freely accessible for mechanical examination. Moreover, because this receiver is directly connected to the sensory cells, it can be used like a stethoscope to non-invasively probe the functional properties of sensory cells and molecular events in the hearing process.

Although fly and human ears have evolved independently, their auditory sensory cells are developmentally specified by the same gene. This gives a strong suggestion that these cells have both evolved from a common ancestral cell and are accordingly related. Such an evolutionary relation brings about the possibility that hearing in flies and in humans partly relies on the same genes.

Could you elucidate the main functions of the computational model which you are currently developing? How are you hoping this model will further research into the auditory sensory system?

We have devised a physical model of the *Drosophila* ear that quantitatively links the ear's macroscopic performance to molecular events. Using this model, alterations in molecular parameters – such as the number of ion channels which are converting sound into electrical signals and their corresponding single channel gating energies – can be deduced.

The group has recently been successful in using the model to ascertain the molecular identity of such ion channels. However, running the model is very time-consuming, which presents a problem as our aim is to use it to simulate the organs of hundreds of mutant flies. To help accommodate such high-throughput screening, we are currently implementing the physical model in a computational framework which is both easy to handle and able to run at high speed.

Has your laboratory developed any other new tools or methods to probe the auditory system of *Drosophila*?

We have established methods to measure sound-induced vibrations in the *Drosophila* ear and to deduce cellular properties and molecular events. Sound-evoked electrical responses of the fly's auditory neurons can easily be recorded if one sticks an electrode in the fly's antennal nerve. We also expressed genetically encoded calcium sensors in these cells and imaged their intracellular calcium signals in order to probe cellular function without compromising the integrity of the ear.

Can you elaborate on the role of rhodopsins in hearing?

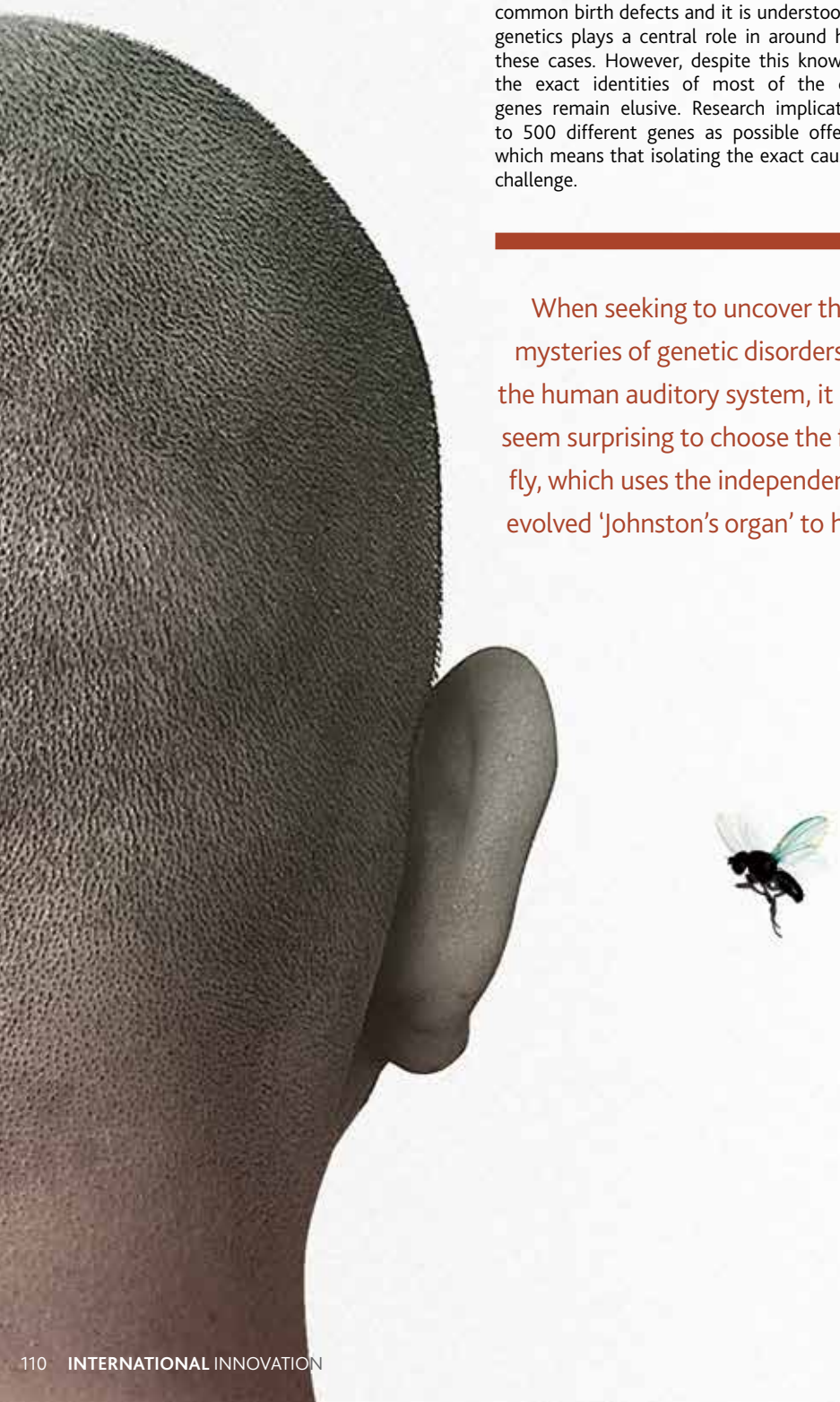
This is what we are now trying to uncover. We found that rhodopsins are present in the fly's auditory sensory cells and that they sit roughly at that site of the cells where sound is converted into electrical signals. We also discovered that rhodopsins seem to facilitate the conversion of sound into electrical signals, but how they do this still is unclear. Unlike in the eye, the activation of rhodopsin in the ear seems to be light-independent, and it will be interesting to learn how they are activated instead.

What are the objectives of the 'Sensory Club' and what is your involvement with this forum? How does such a platform assist your research endeavours?

The Sensory Club is a local initiative of a Collaborative Research Centre at the Göttingen Research Campus. It brings together researchers working on a diverse range of topics related to sensory processing, particularly those with a focus on the molecular mechanisms involved. We believe that the Sensory Club provides an exciting platform for discussion of findings and concepts, and also helps to foster important, close scientific collaborations between colleagues. For example, the mouse projects we recently commenced would not have been possible without such partnerships as, although proficient with *Drosophila*, our group had no experience in working with mice models.

Fruitful **inquiry**

Recent research at the **Georg-August-University of Göttingen's Department of Cellular Neurobiology** looking at the underlying genetics of the fruit fly's auditory system has uncovered surprising results on shared genetic heritage



AFFECTING AS MANY as one in every 300 babies, congenital deafness is one of the most common birth defects and it is understood that genetics plays a central role in around half of these cases. However, despite this knowledge, the exact identities of most of the culprit genes remain elusive. Research implicates up to 500 different genes as possible offenders, which means that isolating the exact cause is a challenge.

When seeking to uncover the mysteries of genetic disorders in the human auditory system, it may seem surprising to choose the fruit fly, which uses the independently evolved 'Johnston's organ' to hear

An interesting approach to this problem, which is currently being investigated by Professor Martin Göpfert's group at the Georg-August-University of Göttingen, is to look not at what studies of human genetics can tell us, but rather to explore what can be uncovered by closely analysing and understanding analogous genetic hearing defects in animals. Although much progress has been made through studies focusing on mice, some of the most substantial breakthroughs have emerged from what may initially seem to be an unlikely candidate: *Drosophila melanogaster*, otherwise known as the common fruit fly.

Hearing is known to be prevalent amongst two groups of terrestrial animals, vertebrates and insects. The auditory systems of these groups are understood to have evolved independently, and as a result their structures are strikingly different. Thus, when seeking to uncover the mysteries of genetic disorders in the human auditory system, it may seem surprising to choose the fruit fly, which uses the independently evolved 'Johnston's organ' to hear. Yet an ever-growing body of evidence justifies this selection. It seems that not only is it very likely that the two auditory systems share aspects of genetic heritage, but that they still possess some remarkable similarities. Göpfert's investigations seek to understand these correlations, and exploring the role of genetics in *Drosophila* auditory dysfunction will enable his group to shed light on similar genetic problems in human hearing.

IDENTIFICATION OF GENES

The researchers have already made significant progress in understanding the biomechanical, cellular and molecular mechanisms underlying hearing in *Drosophila*. During pilot studies, the group has compared detailed gene expression profiles of different flies by analysing the differences between insects with and without the auditory organ. This has enabled the identification of 274 genes expressed in the fly's sensory cells or in the surrounding supporting cells, and has subsequently confirmed their auditory expression. Following this progress, the Göttingen team has set about establishing whether the expressed genes could play a role in auditory dysfunction by systematically

targeting and mutating relevant genes before testing the auditory system of the fly for defects. Their preliminary results demonstrate that mutations in 27 of the 42 genes tested so far do indeed impair fly hearing.

HUMAN HOMOLOGUES

Having already uncovered a considerable number of genes directly implicated in hearing, Göpfert and his collaborators are confident that as research progresses they will continue to identify more. However, the results extend beyond the humble *Drosophila*; 25 of the 27 auditory-relevant fly genes have human homologues, and, as if to corroborate the group's suspicions, some of these homologous genes have already been implicated in human hearing. Surprisingly, the study also flagged up genes which no one would have predicted to play a role in hearing. A particularly striking example is the visual rhodopsin genes. Rhodopsin proteins, or 'visual purple', are best known for their role in the capture of light in photoreceptor cells, but the results of the Göttingen team's endeavours are unexpected; indicating that loss of rhodopsins greatly impairs not only vision but also hearing.

FACILITATE CONVERSION

Following this boon, the next challenge was to establish the role of rhodopsins in the auditory system, which is an ongoing point of investigation for the project. Having established that rhodopsins occur in the fly's auditory sensory cells, located approximately in the sites where sound is converted into electrical signals, they have now been able to show that, as suspected, this conversion process is affected if one rhodopsin gene is disrupted. Furthermore, when disrupting an additional rhodopsin gene that, in the eye, detects light of a different colour, the sound-to-electrical signal conversion process is completely halted. These findings led to the conclusion that rhodopsins facilitate the conversion of sound into electrical signals, but the manner in which they do so remains unclear, as contrary to their role in the eye, the activation of rhodopsin in the ear appears to be independent of exposure to light.

BUZZING IN THE EAR

The Göttingen group has overcome significant experimental challenges which have led to the development of new methods to measure sound-induced vibrations in the *Drosophila* ear and deduce cellular properties and molecular events, allowing gene product function in the auditory system to be easily assessed. While it has been found that the auditory neuron response to sound in the flies can be readily recorded by attaching an electrode to the antennal nerve, the researchers have also employed genetically encoded calcium sensors to monitor the activity of these cells. Intriguingly, the intracellular calcium signals can be imaged through the cuticlar exoskeleton of the antenna, allowing the investigators to probe cellular function without compromising the integrity of the ear.

SHARED EVOLUTIONARY HERITAGE

Ultimately, Göpfert's research on *Drosophila* may help to elucidate the puzzles that surround similar systems in humans. With this goal in mind, the next step for the group will be to identify novel genes for human hearing. This follows initial experiments which indicate that some of the newly defined *Drosophila* hearing genes also feature in sensory cells in the inner ears of mice. To establish the implications of this, the team will study the effect of disrupting these genes on so-called 'knockout' mice, permitting an assessment of whether the gene is required for correct inner ear functionality.

Aside from the hopes of medical progress, it also seems that the work has interesting implications with respect to the evolution of sensory systems. It was found that in *Drosophila* the gene which specifies auditory sensory cells also initiates the formation of both photoreceptors in the eye, and certain olfactory chemoreceptors. This result indicates that all of these systems evolved from a common 'proto'sensory cell, which was probably closest to auditory sensory cells. In support of this, Göpfert's team found that many of the specialised molecules, which photo and olfactory receptors use to detect light and odorants, occur in auditory sensory cells, and have been directly implicated in hearing. This substantiates the claim that these molecules already served sensory functions when the genetic heritages of photo and olfactory receptor cells diverged. Thus, analysing the roles of these molecules in fly hearing may shed light on their ancestral function and offer insight into how sensory cells evolved. The group remains focused on the human consequences, believing that in the long run, this research may help to devise new treatments for hearing impairments, offering hope to those afflicted with deafness.

IDENTIFYING AND CHARACTERISING GENETIC HEARING DEFECTS IN *DROSOPHILA*

OBJECTIVES

- To use *Drosophila* to delineate candidate deafness genes by profiling gene expression in the auditory organ and screening for genetic alterations in function.
- To gain insights into the genetics of auditory stimulus processing, the auditory roles of selected gene products are systematically assessed.

KEY COLLABORATORS

Dr Jonathon Howard, Max-Planck-Institute for Cell Biology and Genetics, Dresden • **Dr Wiebke Möbius**, Max-Planck-Institute for Experimental Medicine, Göttingen • **Dr Andrew Jarman**, Centre for Integrative Physiology, University of Edinburgh • **Dr Daniel Eberl**, Department of Biology, University of Iowa • **Dr Maurice Kernan**, Department of Biology, Stony Brook University • **Dr Jörg Albert**, Ear Institute, University College London • **Dr Azusa Kamikouchi**, Laboratory of Biomolecular Architecture, Nagoya University • **Dr Andre Fiala**, Department of Molecular Biology of Behavior, Göttingen University • **Dr Tobias Moser**, Inner Ear Lab, Göttingen University Medical School

FUNDING

German Science Foundation (DFG, Go1092/1) • Göttingen Collaborative Research Center 'Cellular Mechanisms of Sensory Processing' (DFG, SFB 889) • German Priority Programme 'Ultrafast and Temporally Precise Information Processing: Normal and Dysfunctional Hearing' (DFG, SPP 1608) • BMBF German Bernstein Network for Computational Neuroscience

CONTACT

Professor Martin Göpfert
Full Professor

Department of Cellular Neurobiology
Georg-August-University of Göttingen
Julia-Lermontowa-Weg 3
37077 Göttingen, Germany

T +49 511 177955
E mgoepfe@gwdg.de

MARTIN GÖPFERT is Full Professor for Cellular Neuroscience at the Georg-August-University of Göttingen. He obtained his PhD in Zoology in 1998 and worked as a postdoc at the Universities of Zürich and Bristol. From 2003-08, he headed a Junior Research Group of the Volkswagen Foundation at the University of Cologne. He was awarded the Walther-Arndt Habilitation Prize of the German Zoological Society (2003) and the Biology Prize of the Göttingen Academy of Sciences (2005).