Institution: University of Sussex

Unit of Assessment: 5 Biological Sciences

Title of case study: Diagnosis of the Genetic Causes of Deafness

1. Summary of the impact

About one in 1,000 children are born deaf, and nearly half of all children born deaf have a mutation in one of a number of different genes. Work at Sussex in 1998 on the composition of the tectorial membrane, an extracellular matrix of the inner ear, led to the identification of TECTA as a deafness gene. Because of our research, mutations in TECTA are now known to be a cause of autosomal dominant non-syndromic hearing loss, with 288 affected patients from 51 different families identified worldwide, to date accounting for ~1–2 per cent of all autosomal dominant non-syndromic hearing loss. Critically, TECTA is now one of 60 deafness genes included in genetic tests for hereditary deafness.

2. Underpinning research

The cellular and molecular basis of hearing and deafness has been a focus of research at Sussex for many years. The early work of Russell focused on the electrophysiological properties of sensory hair cells in the cochlea, and was later complemented by the work of Richardson – characterising the key structures required for hearing at a molecular level – and that of Kros, detailing the properties of the different ion channels present in the sensory hair cells of the ear. This work has impacted upon an understanding of how hearing happens, and has revealed the bases of some of the many different forms of sensorineural hearing loss. Studies by Richardson between 1987 and 1995 on the molecular composition of the tectorial membrane, a specialised extracellular matrix that sits on top of the sensory hair cells in the cochlea, revealed that it contains novel matrix molecules that are unique to the inner ear. The subsequent molecular cloning [see Section 3, R1] and mapping of a gene encoding one of these matrix molecules at Sussex, and work performed together with a group in Belgium, identified TECTA, a gene required for normal hearing, as a deafness gene in 1998 [R2]. Mutations in TECTA cause both dominant and recessive forms of deafness, and are now recognised as a cause of autosomal dominant non-syndromic hearing loss [R3]. Mouse models for such deafness-causing mutations made at Sussex have revealed the underlying pathophysiology and isolated specific roles for this matrix in the hearing process [R4]. A number of surface antigens that were first shown, at Sussex, to be associated specifically with the mechano-sensory hair bundles within the inner ear, were subsequently identified as the products of additional deafness genes (PTPRQ, VLGR1 and PCDH15), and the properties of many other hearing loss genes (e.g. MYO7A, STRC, OTOA, ACTG, CCDC50) have been and continue to be characterised by the Sussex hearing team in collaboration with other groups worldwide (R5). Additional studies at Sussex have provided novel insights into the mechanisms of antibiotic-induced otoxicity, revealing, unexpectedly, that the aminoglycoside antibiotics, a commonly used class of medication, selectively enter and accumulate in the sensory hair cells of the inner ear via the transducer channels that are present in these cells [R6].

Key researchers and dates:

- **Guy Richardson FRS**:
  - 2009–present: University Professor, School of Life Sciences, University of Sussex
  - 2004–2009: Professorial Fellow, School of Life Sciences, University of Sussex (Wellcome Trust University Award to G.P. Richardson)

- 1999–2004: Senior Research Fellow, School of Biological Sciences, University of Sussex (PI with salary from Wellcome Trust programme grant to G.P. Richardson)
- 1993–1999: Senior Research Fellow, School of Biological Sciences, University of Sussex (PI with salary from MRC Programme grant to I.J. Russell, G.P. Richardson and C.J. Kros)

- **Corne Kros**:

  - 2005–present: Professor of Neuroscience, School of Life Sciences, University of Sussex
  - 2000–2004: Reader in Neuroscience, School of Life Sciences, University of Sussex
  - 1997–2000: Lecturer then Reader (from 2000) in Physiology, Department of Physiology, University of Bristol
  - 1993–1996: Royal Society University Research Fellow, School of Biological Sciences, University of Sussex
  - 1989–1993: Research Fellow, School of Biological Sciences, University of Sussex

- **Ian Russell**:

  - 1970–2010: Lecturer, Reader then Professor of Neuroscience, University of Sussex

3. References to the research

R1 Legan, P.K., Rau, A., Keen, J.N. and Richardson, G.P. (1997) 'The mouse tectorins: modular matrix proteins of the inner ear homologous to components of the sperm-egg adhesion system', *Journal of Biological Chemistry*, 272(13): 8791–8801.

R2 Verhoeven, K., Van Laer, L., Kirschhofer, K., Legan, P.K., Hughes, D.C., Schatteman, I., Verstreken, M., Van Hauwe, P., Couke, P., Chen, A., Smith, R.J.H., Somers, .T, Offeciers, F.E., Van de Heymning, P., Richardson, G.P., Wachtler, F., Kimberling, W.J., Willems, P.J., Govaerts, P.J. and Van Camp, G. (1998) 'Mutations in human a-tectorin (TECTA) cause autosomal dominant non-syndromic hearing impairment (DFNA8/DFNA12)', *Nature Genetics*, 19(1): 60–62.

R3 Hildebrand, M.S., Morín, M., Meyer, N.C., Mayo, F., Modamio-Hoybjor, S., Mencía, A., Olavarrieta, L., Morales-Angulo, C., Nishimura, C.J., Workman, H., DeLuca, A.P., del Castillo, I., Taylor, K.R., Tompkins, B., Goodman, C.W., Schrauwen, I., Wesemael, M.V., Lachlan, K., Shearer, A.E., Braun, T.A., Huygen, P.L., Kremer, H., Van Camp, G., Moreno, F., Casavant, T.L., Smith, R.J. and Moreno-Pelayo, M.A. (2011) 'DFNA8/12 caused by TECTA mutations is the most identified subtype of nonsyndromic autosomal dominant hearing loss', *Human Mutation*, 32(7): 825–834.

R4 Legan, P.K., Lukashkina, V.A., Goodyear, R.J., Lukashkin, A.N., Verhoeven, K., Van Camp, G., Russell, I.J. and Richardson, G.P. (2005) 'A deafness mutation isolates a second role for the tectorial membrane in hearing', *Nature Neuroscience*, 8(8): 1035–1042.

R5 Lukashkin, A.N., Legan, P.K., Weddell, T.D., Lukashkina, V.A., Goodyear, R.J., Welstead, L., Petit, C., Russell, I.J. and Richardson, G.P. (2012) 'A mouse model for human deafness DFNB22 reveals that hearing impairment is due to a loss of inner hair cell excitation', *Proceedings of the National Academy of Sciences of the Unites States of America*, 109(47): 19351–19356.

R6 Marcotti, W., van Netten, S.M. and Kros, C.J. (2005) 'The aminoglycoside antibiotic dihydrostreptomycin rapidly enters mouse outer hair cells through the mechano-electrical transducer channels', *Journal of Physiology*, 567(2): 505–521.

Outputs can be supplied by the University on request.

Grants supporting, and obtained because of, the underpinning research:

- Russell, I.J., Richardson, G.P. and Kros, C.J. (1 October 1993–30 September 1998) MRC Programme Grant entitled 'The molecular and cellular basis of frequency selectivity and sensitivity in the cochlea' (Value £1,494,217).

- Richardson, G.P. (6 June 1999–31 May 2004) Wellcome Trust Programme Grant entitled 'Cell-surface and extracellular matrix molecules of the inner ear: their roles in hearing, deafness, hair-cell regeneration and deafness' (Value £895,712).

- Kros, C.J. (1 April 2003–31 March 2008) MRC Programme Grant entitled 'Functional significance and developmental acquisition of positional gradients in normal and mutant mammalian hair cells' (Value £815,000).

- Richardson, G.P. (1 July 2004–31 January 2010) Wellcome Trust University Award entitled 'Extracellular-matrix and cell-surface molecules of the inner ear: roles in hearing and hair-bundle development' (Value £1,181,844).

- Petit, C. *et al*. (1 December 2004–31 November 2009) European Union Consortium Grant entitled 'EuroHear' (Value for Sussex [PIs Kros and Richardson] £670,363).

- Richardson, G.P. (1 February 2010–31 January 2015) Wellcome Trust Programme Grant entitled 'The tectorial membrane and the sensory hair bundles of the inner ear: mechanisms of development and effects of deafness-related mutations' (Value £1,268,129).

- Kros, C.J. (PI) with Moore, A.L., Richardson, G.P. and Ward, S. (1 April 2013–31 March 2018) MRC Research Grant entitled 'Mechanisms of aminoglycoside ototoxicity and drug-damage repair in sensory hair cells: towards the design of otoprotective strategies' (Value £2,337,458).

4. Details of the impact

The underpinning research increased our understanding of cochlear function and dysfunction, led to the identification of TECTA as a deafness gene, and revealed roles for many others (e.g. MYO7A, PCDH15, PTPRQ, OTOA & VLGR1). TECTA and the additional genes now comprise a subset of the 60 deafness genes included on OtoSCOPE, a comprehensive genetic test implemented in 2010 and now used for the diagnosis of hereditary deafness by the clinical community [see Section 5, C1, C2 and C3]. Dr Guy van Camp writes: 'The identification of deafness genes has led to improved DNA diagnostics. DNA diagnostics for deafness in children is very important, as it has the potential of providing valuable information on therapeutic options, the future evolution of the hearing loss, the development of additional symptoms (such as blindness in Usher syndrome) later in life, the recurrence risk and guilt relief for parents'.

Between 2008 and 2012, mutations in TECTA have been identified as the cause of hereditary hearing loss in 288 patients from 51 different families worldwide thus far, and the OtoScope screening platform, in the first 100 people tested during this period, has identified two novel missense mutations in TECTA that cause recessive deafness. An understanding of the cause of deafness in these families enables genetic counselling and provides information regarding the suitability of different corrective measures, with hearing aids or cochlear implants being likely therapies. The work has also changed our understanding of how aminoglycoside antibiotics selectively accumulate in and cause damage to sensory hair cells. It thus informs on potential measures to prevent the ototoxic side effects of an otherwise clinically useful class of drug, such as reinforcing the case for a once-daily dosing regime and trying to design novel drugs that could be co-administered with the aminoglycosides and that compete with the antibiotics for the entry mechanism into the sensory hair cells (MRC Research Grant by Kros *et al*.). As a result, we have advised clinicians, during the REF period, about the clinical implications for patients treated with these antibiotics (see Section 5, C4).

5. Sources to corroborate the impact

C1 Letter from Dr Guy van Camp, Department of Medical Genetics, University of Antwerp.

C2 Dr Miguel Angel Moreno Pelayo, Unidad Genética Molecular, Hospital Ramón y Cajal. This source can corroborate that mutations in TECTA are a common cause of autosomal dominant non-syndromic hearing loss.

C3 OtoScope web-site; http://www.healthcare.uiowa.edu/labs/morl/otoscope/home.html

C4 Email from Head of BSUH Audiological Services, to C.J. Kros (dated 19 August 2010).