Institution: University of Sussex

Unit of Assessment: UoA 5 Biological Sciences

Title of case study: Clinical Diagnosis and Management of Xeroderma Pigmentosum and Related Disorders

1. Summary of the impact

Individuals with Xeroderma pigmentosum (XP) are extremely susceptible to sunlight-induced skin cancers and, in some cases, develop neurological problems. Alan Lehmann has developed a cellular diagnostic test for this disorder. This test is now conducted as an integral part of a multi-disciplinary XP specialist clinic in London, which was established as a direct result of Alan Lehmann's research in Sussex and which has led to the improved diagnosis and management of the disorder and an improved quality of life for affected individuals.

2. Underpinning research

The cellular and molecular basis of XP and the related disorders – Cockayne Syndrome (CS) and trichothiodystrophy (TTD) – has formed a major part of Lehmann's research over many years. This work started at Sussex in 1975 and has continued up to the present time. His group first showed that the variant form of XP was deficient in the ability to replicate UV-damaged DNA and that CS cells failed to restore RNA synthesis after UV-irradiation, leading to the discovery of a defect in transcription-coupled repair in this disorder. TTD cells, like XP cells, were shown to be defective in the ability to remove UV photoproducts from cellular DNA. Based on the cellular deficiencies in DNA repair in these disorders, elucidated in his and other labs, Lehmann developed cellular tests specifically for diagnostic purposes [see Section 3, R1].

More recently his research progressed to analysing the genes involved in these disorders and identifying the causative mutations in many affected patients. Defects in any of eight different genes can result in XP. Initially Lehmann focused on the *XPD* gene, defects in which can result in a wide variety of phenotypes, namely XP, TTD, XP with CS, and XP with TTD. Mutations in this gene were identified in patients with TTD [R2] or XP [R3]. The important conclusion from these studies was that the exact site of the mutation determined the clinical phenotype. Mutation analysis was next conducted on the *POLH* gene defective in XP variants, and mutations were identified both in the catalytic part of the Polη protein and in the C-terminal extension affecting protein localisation [R4].

Patients defective in the *XPA* gene are generally extremely severely affected with both skin and neurological abnormalities. A 60-year-old XP-A patient with mild skin symptoms and no neurological problems was found to have a mutation resulting in the abnormal splicing of the XP mRNA. However, a small amount of normal splicing was observed and the resulting minimal residual repair was sufficient to prevent the onset of neurological problems [R5]. This mutation was subsequently found in several XP patients and enabled an optimistic prognosis to be made in these individuals. More generally, the mutation analyses have resulted in more accurate prognoses, ascertainment of carrier status in affected families, and improved prenatal diagnoses.

3. References to the research

R1 Lehmann, A.R., Thompson, A.F., Harcourt, S.A., Stefanini, M. and Norris, P.G. (1993) 'Cockayne's Syndrome: correlation of clinical features with cellular sensitivity of RNA synthesis to UV-irradiation', *Journal of Medical Genetics*, 30(8): 679–682.

R2 Broughton, B.C., Steingrimsdottir, H., Weber, C. and Lehmann, A.R. (1994) 'Mutations in the

xeroderma pigmentosum group D DNA repair gene in patients with trichothiodystrophy', *Nature Genetics*, 7(2): 189–194.

R3 Taylor, E.M., Broughton, B.C., Botta, E., Stefanini, M., Sarasin, A., Jaspers, N.G.J., Fawcett, H., Harcourt, S.A., Arlett, C.F. and Lehmann, A.R. (1997) 'Xeroderma pigmentosum and trichothiodystrophy are associated with different mutations in the *XPD* (*ERCC2*) repair/transcription gene', *Proceedings of the National Academy of Sciences of the USA*, 94(16): 8658–8663.

R4 Broughton, B.C., Cordonnier, A., Kleijer, W.J., Jaspers, N.G., Fawcett, H., Raams, A., Garritsen, V.H., Stary, A., Avril, M.F., Boudsocq, F., Masutani, C., Hanaoka, F., Fuchs, R.P., Sarasin, A. and Lehmann, A.R. (2002) 'Molecular analysis of mutations in DNA polymerase eta in xeroderma pigmentosum-variant patients', *Proceedings of the National Academy of Sciences of the USA*, 99(2): 815–820.

R5 Sidwell, R.U., Sandison, A., Wing, J., Fawcett, H.D., Seet, J.E., Fisher, C., Nardo, T., Stefanini, M., Lehmann, A.R. and Cream, J.J. (2006) 'A novel mutation in the XPA gene associated with unusually mild clinical features in a patient who developed a spindle cell melanoma', *British Journal of Dermatology*, 155(1): 81–88.

Outputs can be provide by the University on request.

4. Details of the impact

Xeroderma pigmentosum (XP), Cockayne Syndrome (CS) and trichothiodystrophy are genetic disorders caused by a deficiency – in affected individuals – in the ability to repair damage produced in cellular DNA by ultraviolet light. Although these disorders have a devastating effect on the affected families, in many cases, access to clinical needs have been unsatisfactory due to a lack of clinical expertise. Consequently, Lehmann played an instrumental role in establishing a multi-disciplinary clinic to alleviate this problem, initially in Worthing with Dr Arjida Woollons (an MD who trained in Lehmann's laboratory) but, since 2008, in London, under the clinical leadership of Dr R Sarkany [see Section 5, C1: Letter from Dr Sarkany – 'The Department of Health team (NCG) who annually audit the Service, has commented in each audit on the excellent and symbiotic relationship between Prof. Lehmann's team of research scientists and our multidisciplinary clinical team, which contributes to the standard of patient care in this Clinical Service'].

Since April 2010, following the receipt of funding from the NHS National Commissioning Group (NCG), the clinic takes place every two weeks at St Thomas' Hospital [C2]. Three or four patients spend the whole day at the clinic and receive detailed examination and advice from different specialists. Almost all (approximately 90 per cent) XP patients in this country are now seen at this clinic, which Lehmann attends as Consultant Scientist and where he provides genetic expertise and guidance. This has led to improved patient management and quality of life, as indicated by the questionnaires completed by each patient, detailing patient satisfaction (e.g. 'The whole service was excellent. Could not fault it') and the report from the clinic to the NCG [C3, C4]. The attendance of patients at the XP clinic has resulted in improved photoprotection, especially for children. In 60–75 per cent of families with XP children, the patients wear a UV-protective visor, and UV-protective film has been installed in both home and school. Skin cancers are identified and excised at a very early stage. There is also an increased awareness of the importance of eye photoprotection.

As part of this clinic, Lehmann conducts diagnostic testing in Sussex using simple assays based on his underpinning research into DNA repair [see Section 3, R1 and Section 5, C5, C6]. These tests provide unambiguous confirmation or exclusion of the clinical diagnoses, which has been vital for patient management, both within the clinic and externally, worldwide. For example, he received over 300 samples in the current REF period (2008–2013), from which he has diagnosed about 60

positive cases of XP, CS or TTD. His tests are also used for prenatal diagnoses and, to date, he has carried out over 70 prenatal diagnoses in families with CS, including 10 in the current REF period. Professional/end-users who can corroborate the impact of his input are listed below. A letter from the founder of the XP patient support group says: '...As the Group grew it was quite clear that level of care received by families was not consistent and care seemed to range from negligent to excellent. We soon realised that a minimum standard of care was needed for all XP Patients and with the help of Dr Arjida Woollens and Professor Lehmann, an experimental Multi-disciplinary team was set up at Southlands Hospital. The patient experience was excellent'…The patient satisfaction questionnaires show that the service is very well received…' [C7]. It also attests to the impact on patients and their families by describing how Professor Lehmann "has brought the science to our families and made us more connected with what is going on with our children" [C7].

5. Sources to corroborate the impact

C1 Letter from Dr Sarkany (available on request)

C2 Hospital websites:

- http://www.guysandstthomas.nhs.uk/our-services/dermatology/specialties/xp/team/team.aspx
- http://www.guysandstthomas.nhs.uk/our-services/dermatology/specialties/xp/patients/patient-leaflets.aspx

XP support group website: http://xpsupportgroup.org.uk/?page_id=9

C3 Patient questionnaires detailing patient satisfaction with the clinic.

C4 National Specialised Commissioning Highly Specialised Services Half-year Report

C5 Referral letters from clinicians (available on request)

C6 Diagnostic results letters to clinicians

C7 Individual users who could be contacted by the REF team to corroborate claims:

- Head of the National (NCG) Xeroderma pigmentosum Clinical Service, St Thomas' Hospital, London.
- Letter from Trustee and Founder of the XP Support Group.