Institution: University of Sussex

Unit of Assessment: 5 – Biological Sciences

Title of case study: Enhancing clinical diagnosis and management of Xeroderma Pigmentosum, Cockayne Syndrome and trichothiodystrophy

Period when the underpinning research was undertaken: 2000 – 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof Alan Lehmann	Professor of Molecular Genetics	1973 – ongoing

Period when the claimed impact occurred: 2013 – 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Individuals with Xeroderma pigmentosum (XP), Cockayne Syndrome (CS) and trichothidystrophy (TTD) are extremely susceptible to sunlight and, in many cases, develop neurological problems. Furthermore, people with XP are very sensitive to sunlight-induced skin cancers. Alan Lehmann has carried out research on and developed cellular diagnostic tests for these disorders. These tests are now conducted as integral parts of multi-disciplinary specialist clinics in London, which were established as a direct result of Alan Lehmann's research at Sussex and which have led to the improved diagnosis, management and prognostic predictions of the disorders and an improved quality of life for almost all affected individuals in the UK.

2. Underpinning research

The cellular and molecular basis of XP, CS and TTD – has formed a major part of Lehmann's research at Sussex over many years. 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. 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. Subsequently his research has analysed the genes involved in these disorders and the causative mutations in many affected patients [R1].

The XP multidisciplinary clinic was established in 2010 with Lehmann as consultant scientist and 110 patients are now seen on a regular basis. Analysis of this patient cohort has provided many new insights. Patients defective in the *XPA* gene are generally extremely severely affected with both skin and neurological abnormalities, but a group of patients 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. This mutation has been found in several XP patients and has enabled an optimistic prognosis to be made in these individuals [R2].

Long term studies of 89 XP patients by the XP team at the clinic [R3], the largest reported cohort under long-term follow-up, has revealed unexpected clinical heterogeneity dependent on the affected gene and the exact mutation. An unexpected finding was that three of the genetic XP groups do not show the acute sunburn-sensitivity generally considered a hallmark of the disorder [R4]. Our findings provide improved clinical management and more definitive prognostic predictions as well as providing new insights into the mechanisms of carcinogenesis, ocular surface disease, and neurodegeneration.

The Lehmann lab has been carrying out cellular diagnoses of CS and in collaboration with other groups has identified many mutations in the two CS genes in 124 CS patients [R5]. Again, as a

result of this Sussex research and diagnostic work on CS, a CS and TTD clinic was established in 2019 along similar lines to the XP clinic, with Lehmann as Consultant Scientist.

3. References to the research

R1 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 η in xeroderma pigmentosum-variant patients", Proceedings of the National Academy of Sciences of the USA, 99(2): 815–820. DOI: https://doi.org/10.1073/pnas.022473899 188 Citations

R2 Sethi, M., Haque, S., Fawcett, H., Wing, J.F., Chandler, N., Mohammed, S., Frayling, I.M., Norris, P.G., McGibbon, D., Young, A.R., Sarkany, R.P.E., **Lehmann, A.R.,** Fassihi, H. (2016) "A Distinct Genotype of XP Complementation Group A: Surprisingly Mild Phenotype Highly Prevalent in Northern India/Pakistan/Afghanistan", Journal of Investigative Dermatology, 136(4): 869-872 DOI: https://doi.org/10.1016/j.jid.2015.12.031 11 Citations

R3 Fassihi, H., Sethi, M., Fawcett, H., Wing, J., Chandler, N., Mohammed, S., Craythorne, E., Morley, A.M., Lim, R., Turner, S., et al. **Lehmann, A. R.** (2016). "Deep phenotyping of 89 xeroderma pigmentosum patients reveals unexpected heterogeneity dependent on the precise molecular defect". Proceedings of the National Academy of Sciences of the USA 113(9), E1236-1245. DOI: https://doi.org/10.1073/pnas.1519444113 106 Citations

R4 Sethi, M., **Lehmann, A.R.**, Fawcett, H., Stefanini, M., Jaspers, N., Mullard, K., Turner, S., Robson, A., McGibbon, D., Sarkany, R., Fassihi H. (2013) "Patients with xeroderma pigmentosum complementation groups C, E and V do not have abnormal sunburn reactions." British Journal of Dermatology, 169(6): 1279-1287. DOI: https://doi.org/10.1111/bjd.12523 58 Citations

R5 Calmels, N., Botta, E., Jia, N., Fawcett, H., Nardo, T., Nakazawa, Y., Lanzafame, M., Moriwaki, S., Sugita, K., Kubota, M., Obringer, C., Spitz, M.A., Stefanini, M., Laugel, V., Orioli, D., Ogi, T., **Lehmann, A.R.** (2018). "Functional and clinical relevance of novel mutations in a large cohort of patients with Cockayne syndrome" Journal of Medical Genetics, 55(5): 329-343. DOI: 10.1136/jmedgenet-2017-104877 26 Citations

Citation data from Google Scholar.

4. Details of the impact

XP, CS and TTD are genetic disorders caused by a deficiency 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. The principal impact in this case study is the running of multi-disciplinary specialist clinics for these disorders, established as a direct result of Lehmann's research. These clinics have led to improved diagnoses, prognoses, management and quality of life for affected individuals.

In recognition of both Lehmann's research and his role in these clinics, he was awarded a CBE in 2020 for "Services to Medical Science, Patients and Families affected by Xeroderma Pigmentosum and Cockayne Syndrome" [S1].

Lehmann played an instrumental role in establishing the multi-disciplinary clinic for XP, [text removed for publication], and as part of these clinics, Lehmann conducts diagnostic testing in Sussex using simple assays devised from his research into DNA repair. These tests provide unambiguous confirmation or exclusion of the clinical diagnoses. Following the receipt of funding from the NHS National Commissioning Group (NCG), the clinic takes place every 2 weeks at the Rare Disease Centre at St Thomas's Hospital [S3]. Three or four patients spend the whole day at the clinic and receive detailed examination and advice from different specialists. The numbers of patients attending the clinic has increased from 70 in the first years to about 110 in 2020, this comprises more than 90% of the XP patients in the UK. Lehmann attends the clinic as Consultant Scientist and provides genetic expertise and guidance.

[text removed for publication]

The ability of mutation analyses to provide more accurate prognoses [R2-R4] is a major advance. These analyses also offer ascertainment of carrier status in affected families and improved prenatal diagnoses. His contribution to patients' and their families' understanding and management of the condition is attested to by Sandra Webb, founder of the XP Support Group:

> "Alan has continued with making the science understandable, he wrote the "The Genetics of XP" for our patient information pack. He has attended almost every one of our annual Owl Patrol weekend residential camps ... Through the camps Alan has introduced us to scientists and researchers from all over the world and still continues to make science understandable to our families" [S4].

The quality of patient management is also indicated by the questionnaires completed by each patient [S5], which asks them about the benefits they experienced from using the service; alongside high satisfaction levels, patients also reported increased understanding of the condition and capacity to manage it (e.g. "I know I am in expert, kind and extremely professional hands"; "I learnt a lot of information about the neurological effects of XP"; "Helps to keep my mind at rest"; "Prevention and care, lots of help and advice") [S6]. A report from the clinic to the NHS National Commissioning Group [S7] was favourably received by NHS England: [text removed for publication].

As a result of Lehmann's long-standing research in the area, in 2019 a second multidisciplinary clinic – the CS/TTD Highly Specialist Service at Guys' and St Thomas' Hospital – was established using the XP clinic's successful model as its basis. Lehmann is Consultant Scientist for this clinic also. Though still in its infancy, 45 patients have already attended, and it is anticipated that similar numbers to those for XP will eventually attend. Families, who previously were seen by clinicians with no knowledge of the disorder, are now seen and analysed by a group of expert clinicians and scientists, who know and understand the disorder. The importance of this is evidenced by extremely high patient satisfaction (e.g. "It was our absolute pleasure to meet such an amazing group of doctors and professionals, who treated us with the upmost respect and dignity. The outcome we gained was priceless"; "Highly recommend this clinic – it is fabulous and so good to take with people who understand, the team are fantastic"; "It was amazing to speak with people who actually have knowledge of our child's illness. We are extremely grateful to everyone who worked so hard to get this clinic in place" [S9]).

Dr Shehla Mohammed, Consultant in Clinical Genetics, who established the clinic and is its clinical lead, outlines the "key role both [Lehmann] and his laboratory have played in enabling the establishment and delivery of a comprehensive DNA repair service to patients with complex needs." She expands:

> "Professor Lehmann's vast knowledge and expertise of DNA repair has played a pivotal role in enhancing our understanding of the varied clinical presentation of Xeroderma Pigmentosum (XP) as well as in Cockayne syndrome (CS) and Trichothiodystrophy (TTD). He has provided very valued input in establishing National Highly Specialist clinical services for these conditions. In addition, the availability of functional analysis in Professor Lehmann's laboratory uniquely complements the diagnostic genetic testing at GSTT and provides vital insight into many of our challenging cases."

She adds:

> "I am immensely grateful for Alan's support in helping me to articulate the need for a dedicated National Highly Specialist Clinical service for CS and TTD patients to NHSE, drawing upon our combined and long established diagnostic and clinical expertise in this arena. After many prolonged and challenging discussions, the funding for this service was agreed. This the first service of its kind globally for these disorders … Alan attends these monthly clinics in his role as an expert clinical scientist and as a key member of the multidisciplinary team, to provide unique input into improving patient care. …Alan has an exceptional ability to draw upon his extensive experience and strong patient advocacy skills in working closely not only with the clinical teams at GSTT but also with '*Amy and Friends'*, the patient support group for CS/TTD." [S10]

The importance of the XP clinic was underscored by its winning the British Medical Journal 2019 Dermatology Team of the year [S11].

5. Sources to corroborate the impact

S1 Alan Lehmann was awarded a CBE in the 2020 New Year Honours list for "Services to Medical Science, Patients and Families affected by Xeroderma Pigmentosum and Cockayne Syndrome". PDF https://www.thegazette.co.uk/notice/3454767

S2 [text removed for publication]

S3 Hospital websites:

- https://www.guysandstthomas.nhs.uk/resources/patient-information/dermatology/xp/xeroderma-pigmentosum-clinic.pdf
- https://www.guysandstthomas.nhs.uk/our-services/dermatology/specialties/xeroderma-pigmentosum/overview.aspx
- XP support group website: https://xpsupportgroup.org.uk
- Amy and Friends CS Support group website: https://amyandfriends.org/

S4 Letter from Sandra Webb, Trustee and Founder of the XP Support Group. 11 May 2020. PDF

S5 Copy of XP Patient Satisfaction Questionnaire. PDF

S6 XP Support Group patient feedback 2020. PDF

S7 National Specialised Commissioning Highly Specialised Services Half-year Report 2020. PDF

S8 [text removed for publication]

S9 Letter from Jayne Hughes, Founder and co-ordinator of Amy and Friends CS Support Group. 7 May 2020. PDF

S10 Letter from Dr Mohammed, Consultant in Clinical Genetics & National Lead For CS/TTD Highly Specialist Service, Guys' and St Thomas' Hospital. 10 March 2020. PDF

S11 BMJ 2019 Dermatology Team of the Year https://thebmjawards.bmj.com/winners-2019/