Institution: University of Sussex

Unit of Assessment: 5 – Biological Sciences

Title of case study: Enabling clinical diagnosis and treatment of genetic diseases with immune or neurological dysfunction

Period when the underpinning research was undertaken: 2001 – 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:
Keith Caldecott	Professor and Deputy Director of the Genome Damage and Stability Centre	2002 – present
Penelope Jeggo	Professor	1988 – 2001 (Cat. C); 2001 – 2020 (Cat. A) (now Emeritus)

Period when the claimed impact occurred: 2014 – 2020

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

1. Summary of the impact

The Caldecott and Jeggo laboratories at Sussex identify rare genetic diseases caused by hereditary mutations in genes involved in DNA strand-break repair. They diagnose the causative molecular defects in patients with these diseases as a service to clinicians and clinical geneticists in the UK National Health Service and worldwide, who would otherwise be unable to make these diagnoses. Their diagnoses allow appropriate care regimes to be developed. Since 2014, the laboratories have identified the causative defects in more than 100 patients with very rare genetic diseases. The diagnoses and underpinning research benefit patients by enabling better disease management and by enhancing patient care. For example, these diagnoses guide the selection of appropriate therapeutic regimes, identify environmental factors that might reduce or exacerbate disease, reduce the need for prolonged invasive clinical tests, and enable patients to make informed decisions concerning lifestyle choices as well as to better understand and cope psychologically with their disease.

2. Underpinning research

Immunological and neurological disease is crippling and often life-threatening and can result from a variety of hereditary genetic defects. Some of these defects reflect an inability of the affected individuals to process and/or repair DNA damage effectively. The Caldecott and Jeggo laboratories at Sussex are recognized world-wide as experts at the forefront of identifying and characterising the molecular mechanisms by which human cells repair broken DNA, and in understanding how these mechanisms are critical for human health. In particular, as a result of work into fundamental mechanisms of how human cells repair DNA single-strand and DNA double-strand breaks, Caldecott and Jeggo have identified a number of previously unknown human genes which, if mutated, result in hereditary immunological, neurodevelopmental, and/or neurodegenerative disease. The research described in this case study was initiated within the University-based Cell Mutation Unit, in which Jeggo's work was funded by the Medical Research Council (Category C employee); the Unit closed in 2001, but its work was subsequently continued within the University's new Genome Damage and Stability Centre (from which point Jeggo became a Category A Sussex employee, and Caldecott was also employed).

The Caldecott laboratory has identified *TDP1*, *APTX*, *APLF, TDP2, PNKP,* and *XRCC1* as novel human genes involved primarily in the repair of DNA single-strand breaks, and has established

that patients with mutations in any one of these genes succumb to neurodevelopmental and/or neurodegenerative disease [R1–R3].

Similarly, the Jeggo laboratory has identified the genetic basis of diseases associated with combined immunodeficiency and with elevated sensitivity to ionising radiation (RS-SCID), such as those mutated in NBS, XRCC4, Artemis, and DNA ligase IV Syndrome [R4-R6]. These genes are central components of the repair of DNA double-strand breaks – a process that is critical to the development of the immune system and to resistance to X-rays and some types of chemotherapy.

As a direct result of these fundamental discoveries of new DNA repair genes and the roles they play in DNA repair in humans, Caldecott and Jeggo are now frequently approached by clinicians and clinical geneticists in the UK and abroad for advice and diagnostic help for patients, who are often children, with very rare diseases similar to – or the same as – those identified through Sussex research.

3. References to the research

R1 Gómez-Herreros F, Schuurs-Hoeijmakers JH, McCormack M, Greally MT, Rulten S, Romero-Granados R, Counihan TJ, Chaila E, Conroy J, Ennis S, Delanty N, Cortés-Ledesma F, de Brouwer AP, Cavalleri GL, El-Khamisy SF, de Vries BB, **Caldecott KW**. TDP2 protects transcription from abortive topoisomerase activity and is required for normal neural function. *Nature Genetics* (2014) 46, 516-521. DOI: 10.1038/ng.2929 123 Citations

R2 Hoch NC, Hanzlikova H, Rulten SL, Tétreault M, Komulainen E, Ju L, Hornyak P, Zeng Z, Gittens W, Rey SA, Staras K, Mancini GM, McKinnon PJ, Wang ZQ, Wagner JD; Care4Rare Canada Consortium., Yoon G, **Caldecott KW**. XRCC1 mutation is associated with PARP1 hyperactivation and cerebellar ataxia. *Nature* (2017) 541:87-91. DOI: 10.1038/nature20790 137 Citations

R3 Kalasova I, Hailstone R, Bublitz J, Bogantes J, Hofmann W, Leal A, Hanzlikova H, **Caldecott KW**. Pathological mutations in PNKP trigger defects in DNA single-strand break repair but not DNA double-strand break repair. *Nucleic Acids Res*. (2020) 48:6672-6684 DOI: 10.1093/nar/gkaa489 5 Citations

R4 O'Driscoll, M., Cerosaletti, K.M., Girard, P.-M., Dai, Y., Stumm, M., Kysela, B., Hirsch, B.,Gennery, A., Palmer, S.E., Seidel, J., Gatti, R.A., Varon, R., Oettinger, M.A., Neitzel, H., **Jeggo, PA,** and Concannon, P. (2001) DNA Ligase IV mutations identified in patients exhibiting development delay and immunodeficiency, *Molecular Cell*, 8: 1175–85. DOI: 10.1016/s1097-2765(01)00408-7 521 Citations

R5 Woodbine L, Neal JA, Sasi NK, Shimada M, Deem K, Coleman H, Dobyns WB, Ogi T, Meek K, Davies EG, **Jeggo PA**. PRKDC mutations in a SCID patient with profound neurological abnormalities. *J Clin Invest*. (2013) 123:2969-80. DOI: 10.1172/JCI67349 110 Citations

R6 Biehs R, Steinlage M, Barton O, Juhász S, Künzel J, Spies J, Shibata A, **Jeggo PA**, Löbrich M.DNA Double-Strand Break Resection Occurs during Non-homologous End Joining in G1 but Is Distinct from Resection during Homologous Recombination. *Mol Cell.* (2017) 65:671-684. DOI: 10.1016/j.molcel.2016.12.016 139 Citations

Citation data from Google Scholar.

4. Details of the impact

The primary beneficiaries of the impact achieved by this research are the patients [S1-S8]. Typically, clinicians or clinical geneticists contact the Caldecott or Jeggo labs with a request for help with molecular diagnoses and they provide either patient blood and/or skin biopsies from which we establish patient-derived cell lines. With these cell lines, it is possible to assess the integrity of various DNA strand break repair and/or related cellular or biochemical processes to identify the underlying molecular cause of the disease. Thus “novel diagnoses” [S1] can be provided that often [text removed for publication] faced by patients with rare genetic disorders. The work has also been [text removed for publication] in some instances, allowing clinicians to move closer to diagnosing a different rare disease [S5].

The results of the molecular and genetic diagnostic tests are provided to the clinician or clinical geneticist who requested help, who then use that diagnosis and subsequent advice to inform the patient and improve patient care and to facilitate better disease management. Accurate diagnoses are crucial in ensuring safe and effective patient management and care; for example, if not properly diagnosed, standard chemotherapeutic/radiotherapy regimes can be fatal in cancer patients who harbour specific genetic mutations (e.g. in *XRCC1*, *PNKP*, *LIG4*, *TDP2*). This is because individuals with mutations in these genes are hypersensitive to such regimes, as their ability to repair the DNA damage induced by standard chemotherapy and radiotherapy is compromised. Similarly, standard DNA break-inducing conditioning regimes used during the bone-marrow transplantation that is needed to combat the immunodeficiency of LIG4 Syndrome patients can be fatal. Thus, "knowing this information for a particular patient is critical for subsequent management decisions" [S4].

Diagnoses can also help identify environmental factors that might reduce or exacerbate disease [S10], reduce the need for prolonged/ongoing invasive clinical tests [S1], and enable patients to access vital services, such as physiotherapy [S1] or counselling [S2]. They also enable patients to make informed decisions concerning lifestyle choices [S1, S2], to better understand and cope psychologically with their disease [S3], as well as to access support networks connecting families and individuals with the same conditions [S2, S9, S10].

During this REF reporting period, Caldecott and Jeggo have been approached by health care workers (mainly clinical geneticists and clinicians) in hospitals within: the UK National Health Service (NHS) (e.g. Great Ormond Street, Newcastle General Hospital, Royal Free Hospital, London, Glasgow Genetics Dept., MRC Human Genetics Edinburgh, Manchester Christie Hospital); Europe (e.g. IRCM France, Nijmegen Medical Centre Netherlands, Dept. Molecular Medicine, University of Pavia, Children's Hospital Helsinki); the US (Ochsner Medical Centre for Children New Orleans); Canada (Hospital for Sick Children Toronto); Australia (Primary Immunodeficiency Unit, Lisbon); and Russia (Research Center for Pediatric Hematology, Oncology and Immunology Moscow). This has led to the Caldecott and Jeggo laboratories identifying the underlying molecular genetic defects in more than 100 patients with a range of rare hereditary DNA damage-associated diseases.

As an example of such work, at the request of Dr Grace Yoon from The Hospital For Sick Children in Toronto [S1], the Caldecott laboratory identified the molecular defect in patients with a completely new neurodegenerative disease, associated with mutations in the DNA repair gene *XRCC1*. This disease is now formally recognized and designated by the medical community as *spinocerebellar ataxia autosomal recessive 26* (SCAR26) (Online Mendelian Inheritance in Man; https://www.omim.org/about). In a letter, Dr Yoon describes the "importance of our collaboration… not only in establishing novel diagnoses and disease management for my patients, but also in directly advancing patient care," and confirms that the former are "extremely important for clinicians to consider when evaluating patients with these serious neurogenerative diseases". In addition to informing clinicians' treatment decisions, Dr Yoon outlines that "having a genetic diagnosis allows patients to access services… which are otherwise very difficult to obtain. A confirmed diagnosis of a genetic ataxia will also decrease the number of invasive and expensive investigations (e.g. muscle biopsy, MRI) that a patient may undergo as part of the diagnostic process" [S1].

In other examples, at the request of clinical geneticists/clinicians in Canada [S1], [text removed for publication] the laboratories have diagnosed and confirmed the molecular defects in the diseases *rigidity and multifocal seizure syndrome* (mutated in the gene *BRAT1*), *spinocerebellar ataxia autosomal recessive 26* (mutated in the gene *TDP2*), and *microcephaly with early onset seizures* (mutated in the gene *PNKP*), the latter two of which are diseases that were discovered at Sussex. Similarly, during this REF reporting period, the Jeggo laboratory has diagnosed and confirmed the molecular defects in biopsies from patients with mutations in the DNA double-strand break repair genes *NBS1*, *XRCC4*, *Artemis*, and *DNA ligase IV* at the request of clinicians/clinical geneticists from a variety of hospitals in the UK and abroad, who greatly valued the Jeggo lab's "unique knowledge" [S5, S6]. Some of these hospitals have now established Sussex-developed diagnostic tests in-house, under guidance from the Jeggo laboratory, as have a variety of leading medical and clinical genetics centres worldwide e.g. Great Ormond Street

UK, Baylor College of Medicine US, Children's Hospital of Eastern Ontario Canada, Nijmegen Clinical Genetics Center, Belgium, and Neckar-Enfants Malades Hospital Paris.

As a result of this research and diagnostic efforts, Caldecott and Jeggo are also approached by charitable organisations and parent/patient support groups for advice and information about the diseases that they diagnose. For example, Jeggo is a Trustee and Chair of the Scientific Advisory Board of the Ataxia-Telangiectasia (AT) Society (https://www.atsociety.org.uk/), which supports families with individuals suffering from Ataxia-Telangiectasia. Jeggo's role is to provide advice on research strategy and to liaise with both clinicians and scientists. In addition to direct patient support, the Society plays a major role in raising awareness of rare disorders, establishing networks of patients, promoting clinical trials and supporting workshops focusing on the disorder [S9-S11]. The Chair of the AT Society emphasises the importance of the disorder's diagnosis for their work: "without quick and reliable diagnoses we would not be able to support and help improve the lives and care of AT individuals" [S9].

5. Sources to corroborate the impact

S1 Letter from Dr Grace Yoon MD, Hospital for Sick Children, Toronto, Canada. 1 September 2020 [PDF]

S2 [text removed for publication]

S3 [text removed for publication]

S4 Letter from AR Gennery, Professor and Honorary Consultant in Pediatric Immunology + HSCT Translational and Clinical Research Institute, Newcastle University. 30 March 2020 [PDF]

S5 [text removed for publication]

S6 Letter from Giulia Prunotto MD, San Gerardo Hospital, Monza. 21 September 2020 [PDF]

S7 [text removed for publication]

S8 Letter from Dr Sujal Ghosh MD, Clinic for Childhood Oncology, University Hospital, Dusseldorf, Germany. 18 February 2020 [PDF]

S9 Letter from Kay Atkins, Head of Services, AT society. 20 September 2020 [PDF]

S10 Letter from Mike Detsiny, Chair of AT Society. 18 September 2020 [PDF]

S11 AT Society Autumn 2020 Newsletter [PDF]