Institution: University of Aberdeen

Unit of Assessment: UoA1: Clinical Medicine

Title of case study: Thalidomide research guides recognition and compensation for survivors born with Thalidomide damage.

Period when the underpinning research was undertaken: 2009-2018

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:
Neil Vargesson	Professor in Developmental Biology	Aug 2007 - present
Lynda Erskine	Professor in Neurobiology	Aug 2007 - present

Period when the claimed impact occurred: 2011 and onwards

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Thalidomide was given to pregnant women around the world as a treatment for morning sickness in the 1960s, with the result that many miscarried or gave birth to malformed babies. It is still prescribed today for indications including multiple myeloma and complications of leprosy. The team at Aberdeen explored how – and crucially when – thalidomide disrupts limb formation and the range of other forms of damage caused by thalidomide. This research led to expert testimony in a landmark class action lawsuit in Australia in which 107 claimants were compensated over AUD100,000,000. Expert opinion based on the research has influenced international government policy to support thalidomide survivors and identification of hitherto unrecognised people damaged by thalidomide in Canada, Australia and Italy.

2. Underpinning research (indicative maximum 500 words)

Pregnant women in 46 countries given thalidomide for morning-sickness in the 1960s miscarried or gave birth to malformed babies, many of whom died. Surviving infants lived with severe malformations of limbs, eyes, ears, face, genitals, joints and dysfunction of internal organs, aging disorders and nerve damage. In the few years the drug was marketed as safe, the thalidomide disaster, deemed the worst medical atrocity of the 20th century, resulted in over 10,000 affected babies being born in over 46 countries where the drug was licensed. Survivors have lived for decades with severe physical disabilities, discrimination and early onset old-age related disorders, and their families have sacrificed normal lives to provide care.

Aberdeen research conducted by Prof Neil Vargesson and Prof Lynda Erskine using chicken and zebrafish embryos has provided the mechanistic understanding of how thalidomide leads to limb malformation through the inhibition of angiogenesis during development – a process by which new blood vessels are formed and elaborated in developing tissues and organs. The Aberdeen research showed on a cellular level that early embryos exposed to thalidomide suffered loss of newly formed and forming blood vessels, which inhibited limb formation, while more mature blood vessel development is unharmed by thalidomide. The identification of the basis of the time-sensitive nature of the effects of thalidomide, has become a cornerstone in the understanding of thalidomide [**R1**]. The study showed that the loss of newly forming vessels from early embryos resulted in cell death and associated gene signalling, culminating in lack of further limb growth and limb malformation. It also demonstrated how variation and severity of malformation could arise depending on the timing of drug exposure. The research group went on to study the neurotoxic action of thalidomide that has previously been suggested to cause limb malformations, and on which some of the diagnostic criteria underpinning thalidomide embryopathy have been based. The Aberdeen group used a thalidomide analog that causes nerve damage, blood vessel loss and

malformation of limbs [**R2**]. The group demonstrated that nerve loss does not directly cause malformation of limbs, but nerve loss exacerbates the broad damage caused by blood vessel loss, cell death and loss of gene expression.

The group has also investigated new animal models for the study of thalidomide-induced embryo damage including a mammalian model which demonstrates comparable outcomes to those seen in humans [**R3**]. This is vital as rodents, such as mice, which are traditionally used to study drug action, are insensitive to thalidomide. Alternative mammalian models are required particularly for ensuring safety of new analogs as well as to further understand thalidomide molecular interactions in a model much more closely related to humans.

Unravelling the precise mechanisms of the drug is important for current day practice as thalidomide is still used for treatment of multiple myeloma and for complications of leprosy. The research by Prof Vargesson and colleagues at Aberdeen underpins their follow-up work where they addressed the question of how distinct properties of thalidomide and its analogues may contribute to specific clinical outcomes. Prof Vargesson and colleagues' work has shown that thalidomide's ability to inhibit blood vessels is the basis of how the drug causes birth defect. They then set about analysing the effects of a series of thalidomide analogues in vertebrate embryo development, to identify forms of the drug that retain clinical benefit without causing embryopathy [**R4**]. Novel thalidomide analogues, obtained from Prof Vargesson's long-term US collaborators (Figg *et al*), were examined in Aberdeen, and from 81 analogues, they identified 11 lead compounds for further pre-clinical consideration which have solely anti-inflammatory properties with no teratogenic consequences. They also identified 13 compounds with potent anti-angiogenic properties and teratogenic actions that could be useful for cancer treatment in adults. From these studies, the Aberdeen team confirmed their earlier work that inhibiting blood vessel growth causes limb deformity, but that clinically useful analogues could be identified that did not harm embryos, meaning that such analogues would have clinical utility with minimised embryopathic risk. The Aberdeen team has since been granted two patents covering these analogues together with their US collaborators who supplied the thalidomide analogues (Patent application PCT/US2016/054430 filed September 30, 2016 and US patents granted in 2020 (10,730,835 and 10,836,721).

This group's work, exploring thalidomide-induced embryopathy, has created a body of findings that has contributed to understanding how exposure to the drug translates to anatomical outcomes for people born to mothers who were given thalidomide, as well as identifying safe forms of the drug that retain clinical benefit without causing birth defect.

3. References to the research (indicative maximum of six references)

The quality of the research is deemed to be at least of 2* quality as corroborated by the following peer-reviewed, international publications (Aberdeen **researchers in bold,** with **staff bold and underlined** (with Google Scholar **citations**):

[**R1**] Thalidomide induces limb defects by preventing angiogenic outgrowth during early limb formation. **Therapontos C, Erskine L**, Gardner ER, Figg WD, **Vargesson N.** Proc Natl Acad Sci U S A. 2009 May 26;106(21):8573-8. doi: 10.1073/pnas.0901505106. Epub 2009 May 11. (**235**)

[**R2**] CPS49-induced neurotoxicity does not cause limb patterning anomalies in developing chicken embryos. **Mahony C, McMenemy S, Rafipay AJ, Beedie SL, Fraga LR**, Gütschow M, Figg WD, **Erskine L, Vargesson N**. J Anat. 2018 Apr;232(4):568-574. doi: 10.1111/joa.12712. Epub 2017 Oct 10. (**5**)

[**R3**] A new mammalian model system for thalidomide teratogenesis: Monodelphis domestica. Sorensen D, Sackett A, Urban DJ, Maier J, **Vargesson N,** Sears KE. Reprod Toxicol. 2017 Jun;70:126-132. doi: 10.1016/j.reprotox.2017.01.010. Epub 2017 Jan 24. (**6**)

[**R4**] In vivo screening and discovery of novel candidate thalidomide analogs in the zebrafish embryo and chicken embryo model systems. **Beedie SL, Rore HM, Barnett S**, Chau CH, Luo W, Greig NH, Figg WD, **Vargesson N**. Oncotarget. 2016 May 31;7(22):33237-45. doi: 10.18632/oncotarget.8909. (**32**)

Grants supporting the Underpinning Research

Awarded to Neil Vargesson:

University of Aberdeen Kosterlitz Centre for Therapeutics Seedcorn fund; 2008 – 2010; GBP4,000

'Identifying forms of thalidomide with clinical relevance for anti-inflammatory treatments with no teratogenic side-effects' - Wellcome Trust/NIH PhD Scholarship – 2011-2016; GBP70,000

'Screening of thalidomide analogs for anti-inflammatory actions' - NIH Small Award – 2017-2018; GBP19,368.

4. Details of the impact (indicative maximum 750 words)

For decades, the legacy of the thalidomide tragedy has imposed upon the survivors and their families' lives filled with difficulty, pain and discrimination, in some cases without recognition or support. The Aberdeen research findings led to several impacts, including helping to identify and compensate thalidomide survivors, influencing international government responses by informing guidance for thalidomide embryopathy identification, and enhancing understanding of the effects of thalidomide.

Identifying and compensating thalidomide survivors

The group's research findings revealed the drug's actions on blood vessel development, and that a different range of damage can be induced depending on timing of exposure. This research has been used as expert opinion in a landmark case action for Lynette Rowe, an Australian thalidomide survivor in her 50s, born with neither arms nor legs. Distillers, the drug's distribution company, continued to distribute thalidomide in the 1960s for 6 months after warnings were raised, but later, in the face of undeniable links between the drug and the deformed babies, devised a compensation scheme. However, Ms. Rowe was excluded from the compensation scheme due to her having no limbs, rather than partial limbs. Prof Vargesson was called upon by Australian lawyers in 2011 and 2012 to provide expert opinion on the mechanism of thalidomide embryopathy based on his and Prof Erskine's research findings. Their research demonstrated that the claimant's damage could be due to thalidomide, despite not being of the 'classical' recognised diagnostic criteria. The success of this case led to a further class action claim for another 107 disabled claimants in Australia and New Zealand, who received a collective settlement of over AUD100 million in February 2014. [**S1**; **S2**] The large sums settled to the survivors will provide medical care, home adaptations and physical support for the rest of their lives.

Influencing governmental responses and informing guidance for thalidomide embryopathy identification in the wake of thalidomide

Aside from the consequences of the thalidomide disaster from the 1960s, babies are still being born with thalidomide-induced malformations. The drug, although now banned as a morning-sickness treatment, is given for indications including multiple myeloma in the western world and complications of leprosy in South America. At least 35 thalidomide births were identified between 1996 and 2014 in Brazil, where medicine regulation, distribution and safety were lacking, and which identified the need for better diagnostic criteria, medicine safety and regulation. In response, in 2014 the World Health Organization (WHO) brought together an expert team on Thalidomide Embryopathy. Prof Vargesson was invited to be a part of this team and used the research from Aberdeen regarding thalidomide effects on angiogenesis to contribute to the resulting report "Thalidomide Embryopathy: Report of a meeting of experts" [**S3**]. The Medicines Safety Programme Manager at WHO (HQ) explained "*The report will not only assist in the diagnosis of thalidomide embryopathy, it will also provide a model for diagnosing other types of drug-related*

embryopathy" [**S4**]. The WHO Meeting experts also inputted to the production of revised diagnostic criteria for thalidomide embryopathy, to help identify victims - published in 2018 [**S5**]. The WHO report has also been cited in Canadian Parliament investigations into identification of thalidomide survivors [**S6i**] and the establishment of compensation schemes.

This provision of expert advice based on the Aberdeen research has continued to influence and inform government responses to recognising and compensating thalidomide survivors in several countries around the world. In May 2017 Vargesson gave advice to the Canadian Parliament, on the drug's actions and types of damage caused [**S6i**]. The advice is cited in a letter of recommendation from the Chair of the House of Commons Standing Committee on Health to the Minister for Health, which explicitly calls for the government to "err on the side of compassion" and for claimants previously denied access to the Thalidomide Survivors Support Program to "be clinically evaluated to determine, on a balance of probabilities, the likelihood of thalidomide exposure" [**S6ii**]. These recommendations were adopted in the new Canadian Thalidomide Survivors Support Program (CTSSP), launched in 2019 [**S6iii**]. On the basis of his expertise in thalidomide embryopathy research, Prof Vargesson was invited to serve as an Advisor on the CTSSP multidisciplinary committee, assessing applications for recognition and compensation, since August 2019 [**S6iv**]. Hundreds of applications are expected; this change finally opens up access for every Canadian thalidomide survivor, including those previously denied due to non-classical diagnostic criteria. The support available includes a tax-free lump-sum of CAD250,000; annual payments for life; and funding for extraordinary medical assistance for specialized health care and vehicle/home adaptation.

The group's research on thalidomide mechanism of action and the wide range of damage it can cause to embryos was used to inform both the interim and final reports arising from the Senate of Australia Community Affairs Reference Committee Public Hearing in 2019 on support for Australia's Thalidomide survivors. Prof Vargesson took part in the hearing by video conference and is cited throughout the reports (which refer to Committee Hansard, public hearing, Jan 31st 2019 [**S7i**; **S7ii**]) on his discussion of thalidomide embryopathy and the non-classical manifestations possible. The recommendations included a national apology; education programmes to inform clinicians about thalidomide embryopathy; schemes to identify additional survivors; and lump sum, annual payment and home/vehicle modification funding [**S7i**; **S7ii**]. The Australian Government announced in October 2020 their support of the recommendations and commitment to provide compensation: lump sum and annual payments; health and living support costs; and to establish an eligibility scheme to identify as-yet unrecognized thalidomide survivors, akin to other nations [**S7iii**].

Prof Vargesson provided advice to the Italian Government in 2019 and to the Italian Thalidomide Network group in 2019 [**S8i**] and 2020 on thalidomide embryopathy, focusing specifically on supporting claimants who have non-classical damage. A book outlining the Italian Thalidomide Network Group's work, including the proceedings of a Conference held in February 2020 at which Prof Vargesson presented, is being produced [**S8ii**] and is aimed at further highlighting the needs of thalidomide survivors for support. Prof Vargesson is contributing to the book to explain that thalidomide causes far broader damage than currently recognized. This advice again builds upon the current understanding of the damage patterns which have been delineated by the Aberdeen research, the history of the diagnostic criteria and current viewpoints.

Developing learning material for clinicians

In Australia, one of the recommendations in the Senate report on support for thalidomide survivors [**S7i**] was aimed at improving clinician awareness around thalidomide injuries. In response to this recommendation, Prof Vargesson was enrolled by the Australian government in 2019 as Advisor and Subject Matter Expert to the Royal Australasian College of Physicians (representing over 25,000 medical specialists and trainee specialists) for the development of an eLearning resource on thalidomide and thalidomide injuries to support the education of clinicians and medical professionals [**S9**]. Vargesson created and developed learning objectives, historical overview of the drug, overview of the diagnostic criteria and devised self-assessment tools to test the reader's understanding [**S9**].

In the USA, journalists have called on Vargesson's expertise in a series of articles for the New

York Times highlighting the 'forgotten' alleged thalidomide survivors in the US and their ongoing quest for recognition and compensation [**S10**] and led to communications between Prof Vargesson and the US Thalidomide Association. Vargesson in Sept 2020 presented an online seminar to the US survivors group, discussing his research and advising on how to engage politicians, with survivors from USA, UK and Canada joining the call [**S11**].

5. Sources to corroborate the impact (indicative maximum of 10 references)

S1. Testimonial from Gordon Legal
S2. BBC news article – Thalidomide lawsuit settled in Australia, NZ for AUD81m
S3. WHO report (2014) – Thalidomide Embryopathy: Report of a meeting of experts
S4. WHO media note (portal for medicines webpage)
S5. A clinical review and introduction of the diagnostic algorithm for thalidomide embryopathy
S6. Thalidomide in Canada:
i. Canadian House of Commons 09 May 2017
ii. Letter from Chair of the House of Commons Standing Committee on Health to the Minister for Health
iii. Canadian Government news release
iv. E-mail invitation to Canadian CTSPP advisory role
S7. Parliament of Australia
i. Australian Senate Interim Report February 2019
ii. Australian Senate Final Report March 2019
iii. Australian government response and budget (compensation for survivors)
S8. Thalidomide in Italy
i. Information provided to Italian government
ii. Montecatini Conference
S9. Thalidomide Online Course, Royal College of Australasian Physicians
S10. New York Times article
S11. U.S. Thalidomide Survivors Online Speaker Series