From:
To: Community Affairs, Committee (SEN)
Subject: Re: Submission acknowledgement - Support for Australia's thalidomide survivors
Date: Wednesday, 19 December 2018 3:06:46 AM
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I am a scientist who studies the actions of thalidomide upon vertebrate embryos (in vivo and in vitro) and upon cells (in vitro). We (and others) have shown the drug causes a wide and broad range of damage in vertebrate embryos. We know there is a time sensitive window of action relating largely to the occurrence of outward damage in humans (and vertebrate embryos) (ie damage to limbs, ears, eyes, genitals). We also know internal organs can also be damaged during the time sensitive window (eg: kidney, cardiovascular system, gastro-intestinal tract). This time sensitive window of thalidomide action is in a short period during the 1st trimester of pregnancy. The diagnostic criteria to determine if someone has been damaged by thalidomide exposure were established in the 1960s' – largely by selecting the most severely damaged children to produce the diagnostic criteria that are still used today (this is discussed in Smithells and Newman, 1992; https://jmg.bmj.com/content/29/10/716). However little attention has been paid to understand what might happen if exposure to thalidomide occurs after the apparent time sensitive window of action. Could there be some damage, specifically to internal organ maturation/function only, if exposure occurred in the 2nd or 3rd trimester?.

Recent research (this year – 2018 - in fact) indicates more molecular targets of thalidomide, which after binding with cereblon has been shown to repress SALL4 – (see Matyskiela et al., 2018 *Nature Chemical Biology* volume 14, pages 981–987; Donovan et al., 2018 *eLife*2018;7:e38430 doi: 10.7554/eLife.38430). This is interesting because SALL4 is known to be mutated in a congenital syndrome called 'Duane radial ray syndrome'. This syndrome shares some remarkable similarities to the most severe thalidomide damaged survivors and is often referred to as a thalidomide phenocopy – as they appear so similar and difficult to distinguish apart (for further information on thalidomide phenocopies see Vargesson, 2015 Birth Defects Res C Embryo Today. 105(2):140-56. https://doi.org/10.1002/bdrc.21096). However, the new work on the thalidomide, cereblon and SALL4 interactions was carried out mainly in cell based assays so this interaction needs to be demonstrated in embryos to confirm it causes all the damage. In addition 'Duane radial ray syndrome' does not typically affect legs – which can be affected in some thalidomide survivors… this suggests there maybe multiple targets of thalidomide – which possibly explains the broad and variable damage seen between survivors. Furthermore, just last month another scientific paper indicates thalidomide has potential to bind to 11 other (new, novel) binding targets (Sievers et al., 2018 *Science* Vol. 362, Issue 6414, eaat0572. DOI: 10.1126/science.aat0572). Again illustrating the complexity of this drugs actions. And again indicative that thalidomide embryopathy could be a collection of disorders that can be seen in humans on their own – but in thalidomide embryopathy they can come about together or in combinations (Newman, 1986 Clin Perinatol. 1986 Sep;13(3):555-73; Smithells and Newman, 1992; https://jmg.bmj.com/content/29/10/716) – with the severity likely due to the timing (and perhaps dose) of exposure.

However other important questions remain – how does thalidomide interacting with these molecular

targets then actually cause the range and variability of damage seen in thalidomide survivors? Can these molecular targets of thalidomide explain all the damage and variability of damage between thalidomide survivors? Other widely held theories of how thalidomide causes damage to the embryo include disruption of forming blood vessels, loss of tissue through inducing cell death and nerve damage – so following thalidomide interacting with a molecular target/s, is the actual damage then caused through disruption of blood vessels resulting in tissue loss and/or organ maturation and nerve innervation failure? For a review of the theories of thalidomide mechanism of action/s and some of the current challenges and questions including insights into making clinically relevant but non-teratogenic forms of thalidomide (as the drug is used successfully today to treat conditions like multiple myeloma and complications of leprosy) please see the following two article links (1. Vargesson, 2015 Birth Defects Res C Embryo Today. 105(2):140-56. https://doi.org/10.1002/bdrc.21096; 2. Vargesson, 2019 –J Hand Surg Eur Vol. 44(1) 88-95. https://doi.org/10.1177/1753193418805249).

I have had the pleasure of discussing my group's research with thalidomide survivors at various meetings including The Thalidomide Society annual general meeting in the UK. What strikes me is the range of damage in confirmed survivors – no two survivors look identical. I also presented at a meeting in York in September 2016 to a group of thalidomide survivors, historians and scientists (Newbronner et al, 2017 https://doi.org/10.1002/bdra.23619) – this meeting came to several conclusions – including helping understand the age related changes in thalidomide survivors and how we can treat them better.

I also note that today survivors are suffering from early onset age related diseases – visual impairment, arthritis, internal organ dysfunction – likely due to the change in lifestyle to accommodate their damage (Newbronner and Atkin, 2018 https://doi.org/10.1016/j.dhjo.2017.09.004).