FEATURES

The Vindication of Thalidomide

How modern advances in chemistry and molecular biology have unveiled the therapeutic properties of a birth-defect-inducing sedative.

Image Courtesy of I, Research

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Teratogens are chemical species that can affect fetal development—not quite what the German pharmaceutical company *Grünenthal* had in mind when they synthesized and introduced thalidomide to the market in 1954 as an over-the-counter sedative. Unfortunately, thalidomide became an instant hit among pregnant women suffering from morning sickness, leading to the sale of 14.6 tons of the drug by 1960 in Germany alone (Rajkumar, 2004). It wasn't until 1961, when doctors first reported a link between thalidomide and congenital malformations, that the popular drug was discontinued. Often referred to as the *Thalidomide tragedy*, an estimated 10,000 infants were affected with limb malformations and organ failure worldwide, out of which 40% died within one year of birth (Franks et al., 2004). Decades of clinical research since, however, have resulted in thalidomide becoming a common drug to treat advanced leprosy and even multiple myeloma, a type of blood cancer (Rehman et al., 2011). Moreover,

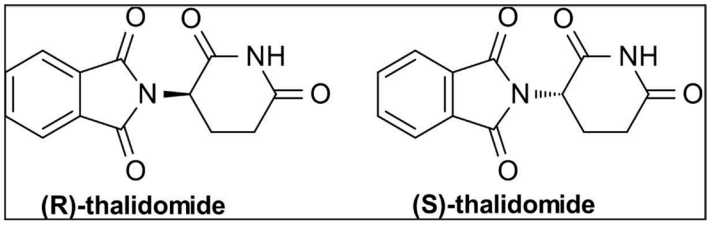
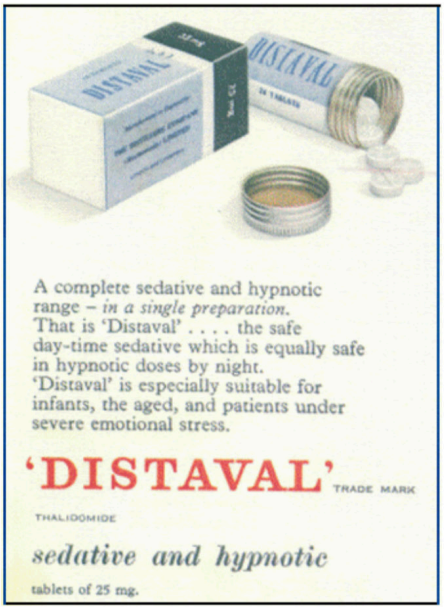


Fig. 1. Thalidomide is a derivative of glutamic acid and it has two distinct stereoisomers: S(-) is the teratogen whereas R(+) functions as a sedative. These variants can interconvert to one another under physiological pH, leading to the double-faced nature of thalidomide (Oxbridge Applications, 2015).

the recent discovery that thalidomide binds to the cereblon protein (CRBN) is paving the way for a new generation of promising small-molecule drugs known as molecular glue degraders. From "one of the worst manmade medical disasters in history" (Robson-Mainwaring, 2019) to a "powerful cancer therapeutic" (Oleinikovas et al., 2023), thalidomide's medical 'vindication' is unprecedented. **How did this happen? What makes it such a promising drug? And what does "vindication" mean for medicine?** This article seeks to introduce the history and science behind these questions.

a)

Distaval thalidomide advertisement, 1961.



b)

Distaval thalidomide advertisement, circa 1961.

Fig. 2. a, b) Thalidomide adverts from 1961 under the commercial name 'Distaval.' They emphasize how thalidomide is safe and non-toxic even when accidentally ingested by children (British Medical Journal, 1961).

Serendipitous Discoveries Paved the Way

Despite thalidomide being effectively banned from European markets in 1961, it continued to be available in countries elsewhere. In 1964, Dr. Jacob Sheskin from the Hadassah Medical Center in Israel reported that a patient's leprosy improved after being administered the sedative (Rehman et al., 2011). This serendipitous discovery reignited Western interest in thalidomide. In the following decades, the use of thalidomide in the U.S. on a controlled experimental basis was approved by the Food and Drug Administration (FDA) for inflammatory skin disorders and graft-versus-host disease, among other conditions (Rehman et al., 2011).

Fig. 3. A thalidomide survivor in therapy at Chailey Heritage in East Sussex. Photograph: Jane Bown

Renewed interest in thalidomide yielded important insights into the structure and properties of the drug. While the molecular pathways of how the drug acts on leprosy patients are not yet fully understood, it is known that thalidomide has anti-inflammatory and anti-angiogenic properties (Rajkumar, 2004). Experts have demonstrated that this inhibition of angiogenesis, or the creation of new blood vessels, is a primary cause of thalidomide-induced birth defects (Therapontos et al., 2009). This property, however, can also be harnessed for good in cancer medicine—as tumors expand, they require a growing supply of nutrients that can only be acquired by creating new capillaries that divert blood flow from organs to the cancer cells. If thalidomide's inhibition of angiogenesis can be targeted toward tumors, the drug becomes a potential new cancer treatment. This realization in the late 1990s kept thalidomide in the spotlight of Western medicine and further incentivized research (Rehman et al., 2011).

In 2010, Dr. Hiroshi Handa from the Tokyo Medical University in Japan serendipitously discovered that thalidomide and its derivatives—now referred to as Immunomodulatory Imide Drugs (IMiDs)—act as

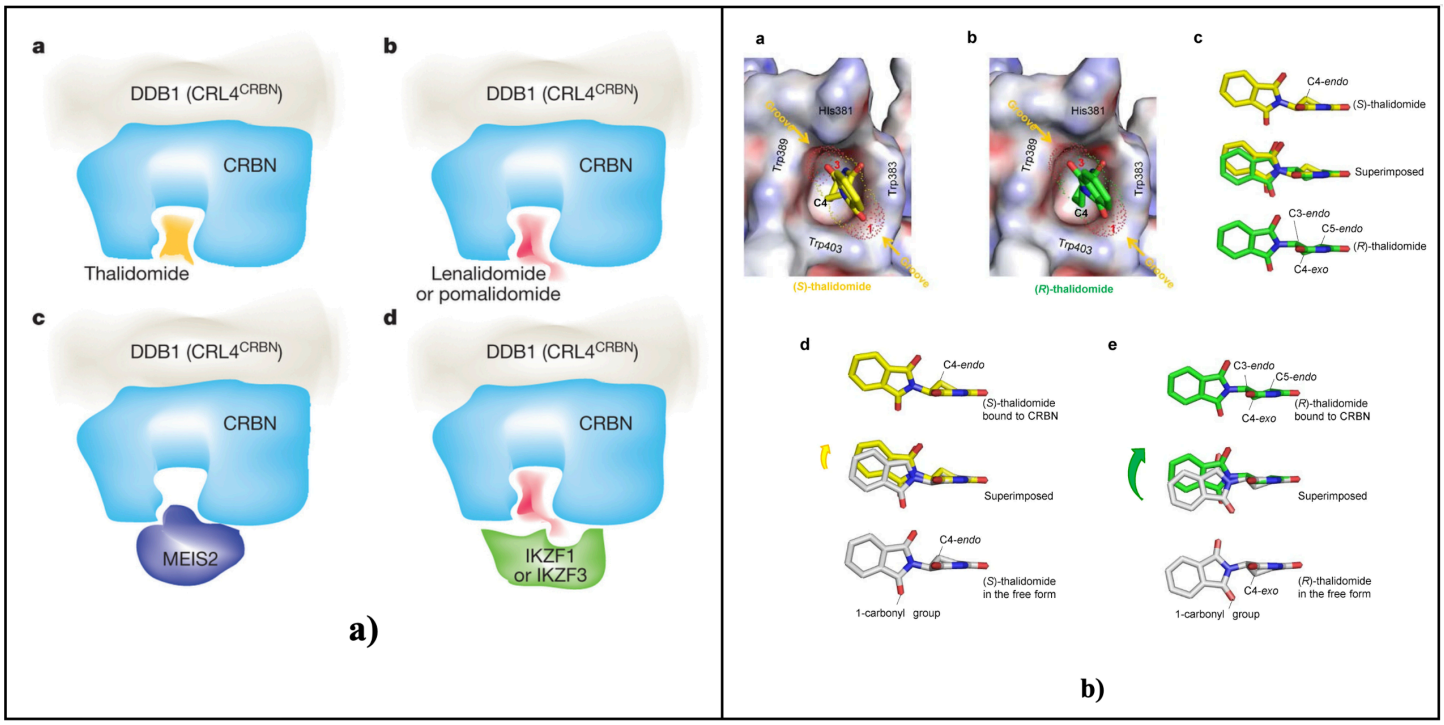


Fig. 4. Binding of thalidomide to CRBN protein. a) Showcases a schematic of different substrates or small molecules that bind to the active site of CRBN, including the molecular glue mechanism of lenalidomide and pomalidomide that binds transcription factors IKZF1/IKZF3 to CRBN (Fischer et al., 2014). b) pyMOL three-dimensional visualization (Mori et al., 2018).

molecular glues that bind to CRBN **(Fig. 4)** (Rehman et al., 2011). This discovery was a scientific breakthrough, as it enabled scientists to interrogate the specific pathways by which thalidomide inhibits angiogenesis. Consequently, the mechanisms under the sought-after functionality of thalidomide—inhibition of angiogenesis—grew less abstract and more accessible to experimental research.

Cellular and Molecular Mechanisms

IMiDs such as lenalidomide bind to the CRBN protein which forms part of a larger E3 ligase complex (Oleinikovas et al., 2023). E3 ligases are enzymes that influence the addition of ubiquitin molecules to specific proteins, essentially flagging them for degradation. The resulting IMiD-E3 complex then binds to different protein targets **(Fig. 4)**, initiating the ubiquitination of a class of proteins called transcription factors, which can regulate the expression of cancer genes (Oleinikovas et al., 2023). To summarize, when an IMiD binds to CRBN, the resulting IMiD-E3 complex triggers the degradation of transcription factors **(Fig. 5)**. The IMiD essentially acts as a "glue" that when bound to CRBN changes the functionality of the larger E3 protein complex.

Molecular glues bind proteins that do not usually interact (Dong et al., 2021). In biology, proteins are complexes of amino acids with distinct shapes that enable them to perform distinct functions within cells. Responsible for a range of varied functions from metabolism to immune reactions, proteins enable the molecular mechanisms necessary for life. Given the complexity of protein-protein interactions in the human body, even molecular changes to the structure of one protein can have cascading effects on its functions and bonds with other proteins. Molecular glues are therefore extremely significant in medicine—if one sticks two proteins together that do not normally interact, they create a protein complex with new and potentially clinically relevant functions.

The binding of thalidomide to CRBN inhibits the proliferation of plasma cells—a type of immune cell—which is extremely useful when trying to inhibit the unregulated proliferation of cancerous plasma cells (Licht et al., 2014). When dealing with cancer cells, aggressive and non-specific treatments like chemotherapy that compromise both cancerous and healthy cells may do more harm than good. Instead, non-aggressive, specific agents have the potential to disrupt the tumors at critical points, thereby setting off a chain of reactions resulting in the death of the cancerous cells. Angiogenesis is often a critical point to be disrupted in the treatment of myeloma, the cancer of plasma cells, given that bone marrow angiogenesis is essential for the progression of this disease (Shu et al., 2022). By restricting angiogenesis through the formation of the IMiD-E3 complex, thalidomide discriminates against cancer without the added toxicity of damaging healthy cells **(Fig. 5)** (Dong et al.., 2021).

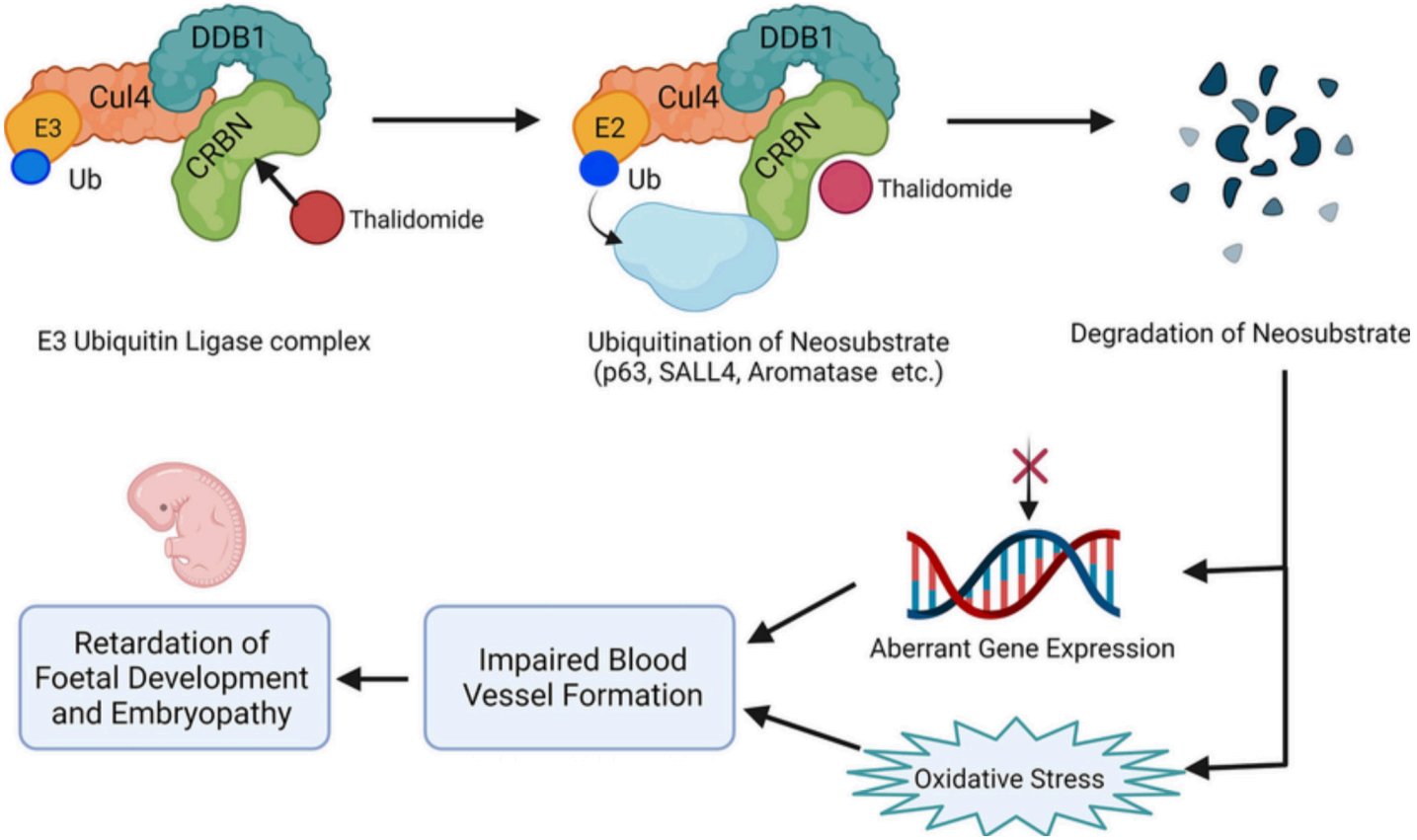


Fig. 5. IMiD-E3 molecular glue degrader mechanism as initiated by the binding of thalidomide to the active site of the CRBN protein. In this context, 'neosubstrate' refers to targets such as transcription factors IKZF1 and IKZF3. Those two factors regulate genes crucial to plasma cell development, hence why their degradation can impair blood vessel formation (angiogenesis) (Gao and Song, 2020).

Applications in Modern Medicine

Thalidomide and its variants can have clinical applications based on their anti-angiogenic properties. If thalidomide's disruption of angiogenesis can be both therapeutic and poisonous, as in the case of thalidomide-induced birth defects, how can we reconcile these differences? How can we make a treatment out of a teratogen? One approach to this problem is to look for other IMiDs that, like thalidomide, possess the elementary features necessary for the restriction of angiogenesis but are not teratogenic. In 2013, experts including Dr. Hiroshi Handa reported that pomalidomide can bind to CRBN stronger than thalidomide and lacks teratogenic effects, making for a much more efficient and safe cancer drug than thalidomide (Mahony et al., 2013).

The steps taken to synthesize thalidomide and unearth its properties represent the trial and error of scientific rationality. Today, scientists have the potential to critically analyze small molecules and devise protocols to turn them into effective drugs. The world has entered the era of rational drug design, where the progression of diseases like cancer can be pinpointed to exploitable molecular targets. The concept is simple: if one knows how the molecular structure of a disease relates to its function, one also can determine what type of small molecule drug might inhibit it. It is an elegant principle that, much like how thalidomide derivatives bind to CRBN and restrict the expression of transcription factors critical for myeloma, focuses on eliminating diseases through specific targeting. If structure begets function in biology, then mutations in structure can beget disease, and inhibitions of said mutations may restore the health of patients without the need to cause off-target damage in non-mutated cells.

Fig. 6. Pomalidomide capsules under the commercial name 'Pomalyst'. Photograph taken by multiple myeloma patient Phillip Jeffrey (2015).

Today, decades of research on thalidomide have yielded important advances in rational medicine. Thalidomide, lenalidomide, and pomalidomide are the three IMiDs that are now globally distributed and routinely used for treating leprosy, multiple myeloma, and lenalidomide-resistant multiple myeloma, respectively. In the U.S. alone, an estimated 35,000 people are affected with multiple myeloma every year (NIH, 2018). Despite the Thalidomide tragedy of the 1960s, the drug continues to impact the lives of thousands of people—this time for the better.

Throughout the article, the history and science of thalidomide were introduced to answer questions about how the drug has resurfaced in the twenty-first century as a cancer therapeutic. It is tempting to envision a transformation of thalidomide from poisonous to therapeutic, but thalidomide's chemical composition is constant. If anything, it is the perception of thalidomide that has been transformed. Serendipitous discoveries, such as those of Dr. Sheskin and Dr. Handa, introduced evidence that challenged experts' perceptions of thalidomide as a toxic, non-therapeutic chemical. The perception of thalidomide has been vindicated; our relationship with chemistry is not static. As scientific advances sharpen our understanding of nature, we learn to vindicate that which we didn't fully understand and exploit it to lead better lives.

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