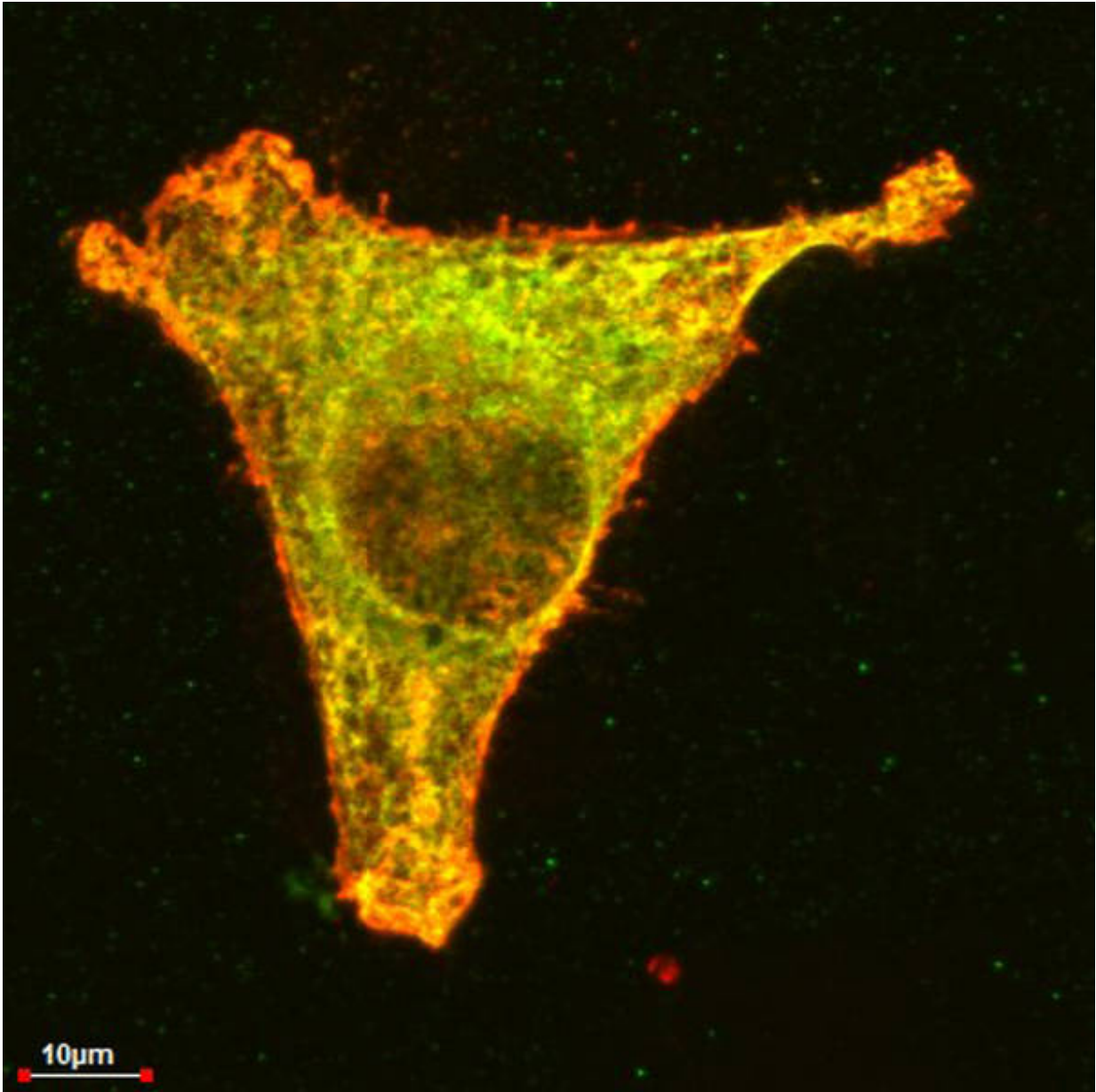


# Scientists discover mechanism of thalidomide

June 17 2016

---



In a tumor cell, thalidomide makes a particular protein complex (highlighted in

yellow) disappear. The same mechanism causes serious malformations in unborn children. Credit: Bassermann/TUM

In the 1950s, thalidomide (Contergan) was prescribed as a sedative drug to pregnant women, resulting in a great number of infants with serious malformations. Up to now, the reasons for these disastrous birth defects have remained unclear. Researchers at the Technical University of Munich (TUM) have at last identified the molecular mechanism of thalidomide. Their findings are highly relevant to current cancer therapies, as related substances are essential components of modern cancer treatment regimens.

Thalidomide was marketed as a sedative in West Germany and some other countries under the brand name "Contergan". 55 years ago, in 1961, it hit the headlines after having caused horrific deformations in unborn children. Between 5,000 and 10,000 children were affected worldwide. To this day, more than 2,000 victims across the world still live with the consequences of this tragedy. Soon after the discovery of these devastating side effects, the drug was withdrawn from the market. More recently, however, thalidomide is experiencing a kind of renaissance, as it was coincidentally discovered to inhibit the growth of certain tumors.

Since then, the two follow-up substances lenalidomide and pomalidomide have been approved for cancer treatment. Both thalidomide-derivatives are successfully used to treat certain bone-marrow cancers such as [multiple myeloma](#). While showing stronger anti-tumor potential, they have fewer side effects than thalidomide. Despite this, they still pose a risk of causing severe [birth defects](#) and must not be taken during pregnancy.

## Several proteins involved

Thalidomide, lenalidomide and pomalidomide are also known as immunomodulatory drugs (IMiDs). The name is derived from their ability to modify the body's immune response. Professor Florian Bassermann at the Department of Internal Medicine III of the TUM University Hospital and his team studied the [molecular mechanism](#) of IMiDs; their study has recently been published in *Nature Medicine*. Bassermann is a Principle Investigator of the German Consortium for Translational Cancer Research (DKTK).

Other research teams had previously established that cereblon, a cellular protein, plays an important role in the function of IMiDs. However, the exact details as to how cereblon mediates the effects of IMiDs have only now been worked out by Prof. Bassermann and his team: Inside cells, cereblon usually binds to the proteins CD147 and MCT1. These two proteins typically occur in blood building and immune cells, and amongst other things, promote proliferation, metabolism and the formation of new blood vessels. In cancers such as multiple myeloma, tumor cells contain particularly high levels of CD147 and MCT1.

## IMiDs "outcompete" proteins

As a so-called [protein complex](#), CD147 and MCT1 always occur as a pair. However, to find their other half and become activated, they require the help of cereblon. Binding to the cereblon protein promotes development and stability of the complex, which in return stimulates cell growth and facilitates the excretion of metabolic products like lactate. In diseases such as multiple myeloma an increased abundance of this protein complex enables tumor cells to multiply and spread rapidly. If such a cancer is treated with IMiDs, the drug virtually displaces the complex from its binding to cereblon. As a result, CD147 and MCT1

can no longer be activated and vanish. "Ultimately, this causes the tumor cells to die," says Dr. Ruth Eichner, the study's first author.

Strikingly, the TUM scientists and a research team from the German Centre for Neurodegenerative Diseases (DNZE) were able to demonstrate that the disruption of the protein complex also causes the devastating birth defects. "The mechanisms are identical," Prof. Bassermann explains. "A specific inactivation of the protein complex resulted in the same developmental defects observed after thalidomide treatment." Without these two proteins, blood vessels cannot develop properly. This confirms the prevailing hypothesis that the typical Contergan-induced deformities are related to the reduced and abnormal formation of new blood vessels.

## **New treatment approaches**

Direct clinical consequences can be drawn from the full correlation of clinical efficacy of IMiD treatment with the observed molecular effects. "The disappearance of the protein complex could only be observed in patients that had responded well to this type of treatment," says Florian Bassermann. This could be helpful in assessing a patient's response before starting the actual treatment: A sample of the patient's [tumor cells](#) could be taken into culture and treated with IMiDs. If these cells then showed a disruption of the complex, the patient will most likely benefit from IMiD treatment.

The results of this recent study also warrant new cancer therapies without IMiDs. The protein complex is a particularly attractive target for tumor treatment, as it is mainly found on the surface of cells and virtually links the inside to the outside of the cell. Therefore, the inactivation of the complex can easily be achieved using specifically produced antibodies and other distinctive drugs - a possibility that is currently being explored by Prof. Bassermann and his team.

**More information:** Ruth Eichner et al, Immunomodulatory drugs disrupt the cereblon–CD147–MCT1 axis to exert antitumor activity and teratogenicity, *Nature Medicine* (2016). [DOI: 10.1038/nm.4128](https://doi.org/10.1038/nm.4128)

Provided by Technical University Munich

Citation: Scientists discover mechanism of thalidomide (2016, June 17) retrieved 1 May 2024 from <https://medicalxpress.com/news/2016-06-scientists-mechanism-thalidomide.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.