Laudation for Georg Winter

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Winner of the Eppendorf Award for Young European Investigators 2019

If you ask students why they intend to pursue a career in biomedical sciences, many of them answer that they want to help developing cures for major diseases. In fact, everyone who has had the unfortunate experience seeing someone close suffering or even dying from a disease understands this motivation: Developing better treatments or novel drugs for therapy, or at least making a small contribution towards this goal, drives many of us forward. We all know about the spectacular successes in drug research such as the serendipitous discovery of penicillin as the first antibiotic. Indeed, both general health and lifespan have dramatically improved over the past 100 years, which is largely due to research leading to new drugs and treatments. In view of such spectacular successes, we forget too often that there are also spectacular failures. In some instances, such failures open the door to completely new and unexpected discoveries. It is one of these cases I will introduce to you, since it directly leads to the research work of this year's winner of the Eppendorf Young Investigator Award.

One of the worst incidents caused by a therapeutic drug was the thalidomide catastrophe, better known to many Germans as the Contergan scandal. Thalidomide was developed in the 50ies by a German company, Chemie Grünenthal. Originally, it was sold over the counter as a "wonder-drug", effective against a large variety of ailments such as pain, sleep problems, gastritis, and nausea. In particular, it was aggressively marketed as convenient treatment against morning sickness common during the first trimester of pregnancy. I guess many of you remember the history: The drug is teratogenic, i.e. it causes massive embryonic malformations on inner organs and limbs. More than 10,000 malformed babies were born worldwide, with the real case number probably being several times higher as many were

not officially counted, particularly in developing countries. More than half of them did not survive, and there are still thousands of affected persons with major disabilities living in Germany alone. I do not want to go into the history how these side effects were discovered and how the company and the various governments dealt with the crisis. Legal battles continue until today - you can look it up in Wikipedia or elsewhere. In any case, after the scandal the drug was "dead" for decades – no researcher dared to touch it. It was not until the early nineties that thalidomide was recognized to be anti-angiogenic and effective in the treatment of certain myelomas. This triggered a revival in research on thalidomide – first somewhat hesitantly, but then with increasing intensity. Several thalidomide derivatives are now in clinical use for treatment of diverse diseases such as leprosy and cancers. They have proven to be effective and rather safe as long as pregnancies during the treatment are strictly excluded.

Despite the steep second "career" of thalidomide as a therapeutic drug, its molecular mechanism of action has remained elusive until a few years ago. To many of you this may sound odd – how can one use a drug without knowing how it works? It helps to remember that in the early days drugs were in wide use for many years before it was understood how they work – in the case of aspirin it took more than 70 years to understand its mechanism!

In 2010, the molecular target of thalidomide was identified by a Japanese laboratory as a protein called cereblon. What is cereblon? It is a unique substrate receptor of a ubiquitin E3-ligase complex. This means that the drug binds to a molecular complex that mediates the destruction of specific target proteins. So how can this help in cancer treatment? It turned out that the drug does not inhibit cereblon but rather changes its substrate preference. In other words, the drug tricks the ligase to earmark proteins for destruction that it does not care about in the absence of the drug.

Let us pause for a second and let us consider what this means. Here we have a drug that does not act by inhibiting an enzyme, receptor, or transporter as most drugs do. Rather, it re-directs an endogenous pathway for elimination of damaged proteins towards elimination of different proteins that are healthy. By chance, these include proteins involved in the development and/or progression of diseases, which explains therapeutic benefits, but they also include transcription factors required for tissue differentiation – hence the malformations. To put it more bluntly: Thalidomide hijacks a cellular destruction machine and steers it towards other than its physiological targets. Intriguingly, certain viruses use similar tricks: For instance, the human immunodeficiency virus (HIV) redirects a ubiquitin ligase towards the surface receptor CD4 in T-cells. Thus, by manipulating an endogenous protein killer complex towards attacking an immune guard post the virus disarms the T-cell – very, very sneaky.

In any case, the mechanism of thalidomide constitutes a novel principle of drug action. These findings set the stage for the discovery of Georg Winter, the winner of the Eppendorf Young Investigator Award 2019. Before Georg tells you more about his work, I briefly want to introduce him to you.

Georg grew up in a small place in Lower Austria, close to the border to the Czech Republic. He then went to Vienna for his university education where he also remained for his PhD work that he carried out at the Research Center for Molecular Medicine (CEMM), under the direction of Giulio Superti-Furga. From the start, as he has told me, he was fascinated by the question how small molecules work in biological systems. In particular he was interested in molecules known for biological effects but whose mechanism of action was not known. During a conference he met James Bradner from the Dana Faber Cancer Institute in Boston who worked on related questions. Georg then applied and joined his laboratory as postdoc for 3 years before returning to Vienna where he is presently leading his own research group.

The work Georg Winter has carried out in Boston is indeed spectacular. He succeeded in converting the ubiquitination system targeted by thalidomide into an extremely promising and general tool for the targeted degradation of specific proteins that is extremely powerful. However, I will let Georg himself explain what this is all about. Let me just mention that his seminal paper in Science has had an enormous impact – it is among the top 1% most frequently cited papers, and it has triggered drug development companies to set up programs worth billions of dollars. Please join me in welcoming Georg Winter, the winner of the Eppendorf Young Investigator Award 2019!