Thomas Wollert wins Eppendorf Young European Investigator Award 2015

Presented in partnership with *Nature*

The Eppendorf Award for Young European Investigators was established in 1995 to recognize outstanding work in biomedical science. It also provides the opportunity for European researchers to showcase their work and communicate their research to a scientific audience. *Nature* is pleased to partner with Eppendorf to promote the award and celebrate the winner's work in print and online. *Nature*'s Julie Gould talks to the 2015 winner Thomas Wollert (Max Planck Institute of Biochemistry, Germany) about his work — which looks at the complex molecular process that cells use to remove their waste — and how it felt to win the award. To listen to the full interview, visit: **go.nature.com/cszfl1**

About the Award

Thomas Wollert is the twentieth recipient of the Eppendorf Award for Young European Investigators, which recognizes talented young individuals working in the field of biomedical research in Europe. The Eppendorf Award is presented in partnership with *Nature*. The winner is selected by an independent jury of scientists under the chairmanship of Reinhard Jahn, Director at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. *Nature* and Eppendorf do not influence the selection. For more information see: **eppendorf.com/award.**

Julie Gould: Congratulations on being awarded this year's prize. How did it feel when you found out that you had won?

Thomas Wollert: That came as a big surprise to me. It's a great honour and it's of course a major recognition of our work; not only my work, but also the work that my laboratory has done over the past five years. So this is very important to me.

JG: Tell us a little bit about the research you are working on.

TW: The cells in our bodies recycle almost everything — they do not waste much. The question in the past has been: how is this achieved? The process needs to be highly regulated. You don't want to degrade something that you still need, but you do want to get rid of dangerous material that accumulates in the cell. We became interested in one pathway that is involved in transporting this sort of trash, or unwanted material, to recycling stations in the cell. We are particularly interested in how the molecular mechanism is driven.

JG: What sort of molecular trash are we talking about?

TW: Everything that needs to be degraded in a cell has to end up at a recycling station, one of which is called the lysosome. What ends up there is chemically degraded, and the building blocks are reused by the cell to build material. Proteins that become aggregated, big material or composite structures, and everything else in the cell cytoplasm (such as mitochondria) need to be transported to the lysosome. There is a specialized pathway to do that — this has been called autophagy for self-digestion. During autophagy, crescent-shaped membranes are formed, which expand and capture cytoplasmic components. These structures become autophagosomes, which are like entire organelles and are the containers that transport the trash to the lysosomes for degradation.

JG: How do these autophagosomes form in the cell?

TW: In yeast the system is fairly well understood. Small membrane vesicles are recruited and fuse to form the crescent-shaped autophagic precursor membrane. This membrane then surrounds and captures material, and, after sealing, the full autophagosome is formed and finally fuses with the lysosome.

There are 40 different proteins in yeast that have been identified as those that have an essential function in autophagy — they are specific to the autophagy pathway. The question was, what are they doing with the membrane and what is their molecular function? And that was the major interest of my lab.

JG: What did you discover?

TW: We analysed two important steps in autophagy. The first is initiation and the second is expansion. During initiation

an autophagosome is built from small vesicles, which come together and fuse. This process is driven by one big complex called the Atg1-kinase complex. This complex is known to be involved in recruiting the donor vesicles that create the autophagosome.

We recently published work on the expansion step. This is an interesting step that involves a small ubiquitin-like molecule, Atg8. The unique feature of this particular molecule is that it becomes covalently attached to autophagic precursor membranes. Many Atg8 molecules get conjugated to these membranes, so the question has been: why is there so much Atg8 on the membrane and what is its job there?

To answer this, we analysed the proteins independently of the complex cellular environment. We produced recombinant molecular machines that drive the formation of autophagosomes and analysed their function in the test tube. The test-tube components include the protein subunits of these molecular machines and model-membranes that serve as the platform for proteins to assemble into large complexes.

What we realized — and what came as a surprise to us — was that the molecular machine that drives conjugation of Atg8 stays with Atg8 at the membrane, rather than leaving after conjugation. We predicted that something needs to happen, some bigger structure needs to form on the membrane to keep the conjugation machine there. Using high-resolution approaches, we observed that Atg8 forms together with its conjugation machine, a protein shell on membranes. It's like a meshwork that sits on top of the membrane and stabilizes the forming autophagosome. Presumably.

JG: Why presumably?

TW: Because the details of how this expansion is driven by the scaffold is something that we are investigating.

JG: Will you be following this up over the next few years?

TW: Yes. This is an interesting question, but not an easy one to answer. We need to understand the direct relationship of how this really works *in vivo*.

Left to right: Wilhelm Plüster, Maria Leptin, Thomas Wollert, Reinhard Jahn, Axel Ziemke and Axel Jahns. Image courtesy of EMBL PhotoLab.

JG: How does the autophagosome capture material from cells?

TW: The selection of cargo comes in two flavours. Under normal conditions, when the cell is happy, it only wants to degrade unwanted material or something damaged. It chooses these materials quite selectively. For example, it might only want to degrade dysfunctional mitochondria, the cell's power plants. The membrane then wraps tightly around these structures.

However, if a cell becomes stressed or starved, it can use autophagy to degrade anything that's around. That means bulk cytoplasm without any selectivity. Imagine a big happy cell that is starved and goes on a low-value nutritional diet. The cell will shrink, but it survives. If nutritional conditions improve, it can grow again.

JG: What big impacts will this research have?

TW: The research focus at the moment is neurodegenerative disease and cancer. In certain neurodegenerative diseases, some proteins can accumulate in cells. There are a couple of diseases, such as Huntington's disease, in which particular genetic modifications lead to alterations in proteins, which then tend to aggregate. In other diseases, such as Alzheimer's disease, proteins also accumulate, and those protein oligomers, or aggregates, are toxic to the cell.

In some neurodegenerative diseases, it has been observed that increasing autophagy is beneficial for cells, and thus patients, because increasing autophagy increases the removal of the toxic material.

Neurodegenerative disease is usually not observed until the later stages, when this material has already accumulated. If you could remove this harmful material from cells, you could maybe rescue some neurons from dying. This is one application where you would really want to increase autophagy.

In cancer, it has already been shown that combining chemotherapy with an inhibitor of autophagy is beneficial because autophagy just counteracts chemotherapy.

JG: What is it about this field that you find so interesting?

TW: What excites me the most is that you can use a minimal system, combining a few components and then trying to get them to work in a test tube. Our major goal, and our holy grail in this research, is to have the full autophagy pathway in a test tube, combining the autophagy components, step by step, to produce an autophagosome from small membranes, and to have some material wrapped in the autophagosome.