

**Laudatio
von
Prof. Dr. Peter Walter**

**anlässlich der Verleihung
des Paul Ehrlich- und Ludwig Darmstaedter-
Preises
2019**

**an
Prof. Dr. Franz-Ulrich Hartl
und Prof. Dr. Arthur L. Horwich**

**Paulskirche, Frankfurt am Main
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Es gilt das gesprochene Wort!

Dear Colleagues, Friends, Family, and Guests.

We're here today in this beautiful, historic place to celebrate the discoveries of two brilliant scientists, Ulrich Hartl and Art Horwich. Together they unraveled a deeply kept secret in the life of proteins. For their amazing accomplishments, we award Art and Ulrich with the 2019 Paul Ehrlich and Ludwig Darmstaedter Preis.

So, you must wonder what Art and Ulrich did to deserve this honor? Indeed, you may ask yourselves what it takes to win this prestigious recognition; is there perhaps a recipe for such success? Well almost ten years ago, Joe Goldstein published such a recipe. In his short piece in *Nature Medicine* titled "How to win a Lasker" award, Joe quoted the British mathematician Godfrey Hardy, who argued in the early 1900's that science should not only be definitive but also be beautiful. Hardy defined "scientific beauty" as an art form in which outstanding science gives you "cerebral chills and intellectual kicks" — that combine the qualities of significance, generality, and unexpectedness. As you will hear, Art and Ulrich's work powerfully reflects these qualities.

Biology, however, is not mathematics, or physics, or chemistry. As biologists, we are not free to impose our own axioms to inject beauty into our work. In biology, Nature presents the playing field, and it is our task to decipher the rules. Disconcertingly, Nature deploys the strategy of randomly trying out new things by mutation and selection, leading to the evolution of the living world that surrounds us. And, then presents us with the most fascinating puzzles to decipher: the inherently unpredictable Rube Goldberg machines that make up a living cell.

Proteins are one of Nature's most marvelous inventions. They are the tiny molecular machines that carry almost all of the important functions in our cells. Without them, there would be no cell, and without a cell there would be no life on this planet. Proteins come in many different shapes, sizes, and functions: they can be enzymes that break down and convert food substances into chemicals useful to nourish our body; they can be tiny molecular motors that generate force to move our muscles; they can be regulators that turn our genes on or off in the right places and at the right time; and they can be signaling machines that transmit information from one of our cells to another. So, proteins are really, really important. They are not just food, as one may be let to believe from nutritional guidelines. The reason why we eat proteins is to break them down into their building blocks so that our cells can make their own new proteins to carry out these marvelous functions.

As you can imagine from this short list of their diversity, proteins are quite complicated large molecules. And there are many of them: each one of our cells makes 1.5 million new proteins every hour, and they all have to be assembled with high quality to maintain our cells in a healthy state. This is a truly monumental task, especially as the molecular environment in our cells is very crowded.

An individual protein is made as a chain of twenty chemically different building blocks that are linked in a particular order. The sequence of the bases in our DNA translates directly into the sequences of the protein chains that it specifies. But a linear protein chain, literally as flexible as a wet spaghetti, would not be of much use. To become useful, a newly made protein chain has to "mature"; that is, it has to compact into a particular three-dimensional shape that, just like a mechanical machine, has working gears, levers, knobs, and switches.

For decades, it seemed that the principles of the protein maturation process were solved. In 1972, the American biochemist Christian Anfinsen shared the Nobel Prize in Chemistry for his discovery that it is the sequence of a protein chain that specifies its three-dimensional shape. In other words, a protein chain of a particular sequence does not need help — it can spontaneously snap into the

correct structure and thus mature all by itself. Anfinsen reached this conclusion by taking an enzyme, unraveling its protein chain at which point it lost all of its useful activity, and watching it regain its function as it refolded into its original shape. This was a major revelation, seductive because of its simplicity. And to date, Anfinsen's observations hold up as the very principle of how proteins attain their shapes.

But often, the path of discovery is paved by surprises. Surprises usually come in the form of paradoxes, experimental observations made by scientists that, in the context of current thinking, do not make any sense. While most people tend to ignore information that does not fit into their preconceived notions, for the curious mind these are moments of great opportunity. This is how Art and Ulrich enter the field of protein maturation.

Art grew up near Chicago. He graduated from Brown University in an unusual program that combined liberal arts with a medical degree. He went to Yale for his residency in pediatrics and worked for many years with patients as a medical doctor specializing in human genetics. Yet, he was always fascinated with basic research, and never gave up working in the lab. He followed this route as a postdoc at the Salk Institute and then moved back to Yale, wanting to understand how cells work and exploit these insights to uncover the molecular basis of what goes wrong in disease. In the course of this work, Art explored a particular protein, ornithine transcarbamylase, a metabolic enzyme that when defective causes a devastating human deficiency. Because this enzyme normally resides in mitochondria, newly made enzyme molecules have to be transported there. On that voyage, it crosses the membranes that surround mitochondria as an unfolded protein chain. Then, as it arrives in the mitochondrion, it will fold into its final shape.

In order to ask what other components in the cell guide the enzyme on its travels from its site of birth into mitochondria, Art turned to bakers' yeast, or as you may prefer to call it, brewers' yeast. These tiny cells can be easily manipulated in the lab and resemble human cells in many aspects, and we have learned a tremendous amount from studying biology in such simpler model systems. Indeed, when Art expressed the human enzyme in yeast cells, it ended up inside mitochondria and carried out its function just fine. Human proteins can indeed be studied in yeast cells and since in yeast it is easy to screen for mutants in which things no longer work, one can deduce which other components in the cell are required for the enzyme to arrive in mitochondria and mature properly. It was this analysis that led to the unexpected - to a paradox: Art found that in yeast cells with a particular mutation, the human enzyme would no longer work. It was made just fine, but it didn't work. He presented this puzzle to his colleagues at meetings, and everyone began wondering what this might mean.

In the audience at one of these meetings was future matchmaker Walter Neupert. Walter was fascinated by the fundamental question of how mitochondria import their proteins - he is one of the very pioneers who discovered many of the mechanism by which this occurs. Impressed by Art's work Walter invited Art to collaborate with his group at the Ludwig Maximilian Universität in München.

Ulrich grew up in the Schwarzwald here in Germany. He studied medicine at Universität Heidelberg but, in contrast to Art, he never practiced medicine. Instead he chose to focus exclusively on research. Indeed, it has been argued that the many a potential patient is much better off because of Ulrich's passion for basic science. Already in Heidelberg, Ulrich was inspired to investigate how proteins travel in cells. His work impressed Walter Neupert, who offered him a position in his group. There, Ulrich turned his attention to the biogenesis of mitochondria and began to work on solving problems related to protein folding. From there his path continued at the University of California in Los Angeles and then at the Sloan Kettering Institute in New York

In Walter's group, Art and Ulrich combined their expertise and together they teased out an answer to the paradox and figure out what went wrong in the mutant yeast. They determined that Art's favored enzyme had indeed arrived at its proper location inside the mitochondrion, but then in the mutant yeast cells got stuck in an unfolded state in which the protein chain did not acquire its final 3-dimensional shape. They reasoned that in the mutant yeast a protein made defective by harboring the mutation was required to help the enzyme fold up properly. And that, of course, was blasphemy, given that Anfinsen with his Nobel Prize winning work had shown that proteins need no helpers to fold. They can do so by themselves, which was the unquestioned gospel at the time.

Controversy and disbelief followed. Yet after the dust settled, it turned out that both ideas are correct. The Nobel committee did not err in giving Anfinsen the prize for the discovery that protein chains contain all the information required to fold by themselves properly, and Art and Ulrich were correct in their assertion that protein folding requires help. The paradox is resolved by the realization that the environment in living cells is incredibly crowded and as such quite different from the test tube experiments that Anfinsen performed. When a protein chain is made inside a cell, it has, like pieces of wet spaghetti, a tendency to stick to each other and jumble up into messy globs that are of no use. What is required are helper proteins that keep protein chains sufficiently isolated and distant from one another, so that they can fold up without sticky distraction. We now call these helpers "molecular chaperones", and just as their human counterparts their role is to prevent a juvenile protein chain from engaging prematurely in inappropriate interactions.

The yeast chaperone defective in the mutant that Art identified is a particularly beautiful example of how chaperones can accomplish their task: Together with the late Paul Sigler at Yale University, Art's lab determined its structure, and Ulrich's lab deduced many of its functional properties. This chaperone turns out to be shaped as a tiny little barrel that can be open or closed by a lid. When it is open, it exposes sticky surfaces on its inside walls and unfolded protein chains are attracted there. Once inside, the lid snaps closed and the barrel walls subtly change to become less sticky. Now the unfolded protein can bounce around inside the barrel until it finds and locks into its own proper shape, just as Anfinsen predicted. But by being isolated in a vessel, the protein chain remains isolated and cannot become entangled with other sticky protein chains. The lid opens and, if time was sufficient, out pops the freshly folded protein. Such insights into the elegant mechanisms of the molecular machines that keep our proteins healthy indeed elicit cerebral chills and intellectual kicks.

With their discovery, Art and Ulrich changed paradigm in biology. We now know that there are over a thousand different proteins that determine the fate of other proteins by nudging them into their proper assembly pathways, or, should they stray from the path, deconstruct them back into their building blocks to start over. Art and Ulrich's work has blossomed into an enormous field, coined "proteostasis" that studies the many interwoven aspects of protein folding and cell health. We now also appreciate that many diseases result from aspect of proteostasis breaking down, especially as we age. After two joint, seminal publications together, Art and Ulrich each pursued separate roads. Over the last few decades, with Art at Yale University and Ulrich back in Germany at the Max-Planck-Institut in Martinsried, their respective labs have explored deep mechanistic questions of protein folding and chaperone function, and how these processes relate to folding diseases such as neurodegeneration in ALS, Alzheimer's and Parkinson's disease with their devastating consequences to patients and society. But it is important to note that neither Art nor Ulrich started out with the intent to study these diseases directly. Their meandering paths were shaped by edler Wissensbegierde, their unwavering desire of wanting to know how cells work and their fearlessness in challenging entrenched ideas.

And today, we celebrate their results, which combine significance, generality, and unexpectedness. Art, Ulrich, congratulations again for your amazing detective work. We eagerly await the next chapters of your adventures.