Horwich Wins Lasker Award by Straddling Science and Medicine



Christopher Capozziello for The New York Times

Dr. Arthur Horwich in his office at the Boyer Center for Molecular Medicine.

By CARL ZIMMER

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NEW HAVEN — Medicine is a divided world. On one side are the doctors, who come face to face with illness each day and try to heal their patients with whatever tools they can get their hands on. On the other are the researchers, who explore the body’s microscopic complexity, never sure whether their discoveries will ever end up in the hands of the doctors.

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Dr. [Arthur Horwich](http://medicine.yale.edu/labs/horwich/), a medical geneticist at [Yale University](http://topics.nytimes.com/top/reference/timestopics/organizations/y/yale_university/index.html?inline=nyt-org), lives in both worlds. “I’ve always been on the fence between science and medicine,” he said. “I could never make up my mind.”

He has spent decades in the company of children, treating them as best he can for potentially fatal disorders. But he has also spent countless hours pondering a microscopic box found in our cells, trying to figure out what happens inside it.

On Monday, the [Albert and Mary Lasker Foundation](http://www.laskerfoundation.org/) announced that Dr. Horwich’s fence-straddling work had earned him this year’s Lasker Basic Medical Research Award with his frequent collaborator, [Dr. Franz-Ulrich Hartl](http://www.mpg.de/378713/biochemie_wissM3) of the Max Planck Institute of Biochemistry in Germany.

Every one of our cells contains thousands of these microscopic boxes, known as HSP60, each measuring a millionth of an inch across. Dr. Horwich and his colleagues discovered that HSP60 is like a changing room for proteins. Once they enter the box, proteins can fold themselves into their final shape so they can begin to do their jobs. It is a transformation we cannot live without: a cell without a gene for HSP60 quickly dies.

“Nobody thought there would be these little nano-compartments in the cell,” said [Dr. Günter Blobel](http://www.rockefeller.edu/research/faculty/abstract.php?id=225), a [Nobel Prize](http://topics.nytimes.com/top/news/science/topics/nobel_prizes/index.html?inline=nyt-classifier)-winning biologist at Rockefeller University who served on the Lasker Award jury. “That is very unexpected and very important and very nice.”

It turns out that misfolded proteins play a role in many diseases, from [Alzheimer’s](http://health.nytimes.com/health/guides/disease/alzheimers-disease/overview.html?inline=nyt-classifier) to [Parkinson’s](http://health.nytimes.com/health/guides/disease/parkinsons-disease/overview.html?inline=nyt-classifier) to [cancer](http://health.nytimes.com/health/guides/disease/cancer/overview.html?inline=nyt-classifier). Dr. Horwich is now investigating how to manipulate HSP60 to fix these errant proteins and potentially treat diseases — eventually, perhaps, sewing his scientific split personality together.

Dr. Horwich, 60, grew up outside of Chicago. As a boy he was a ham radio prodigy, passing the federal exam for a certificate when he was 10. But not long after, physicians who were friends of his father took him on medical rounds, and he knew he wanted to be a doctor.

He got his undergraduate and medical degrees at Brown, then interned at Yale-New Haven Hospital as a pediatrician, eventually returning there as a medical geneticist.

He stumbled across HSP60 quite by accident. In the early 1980s, as a postdoctoral researcher, he studied genetic disorders that disrupted the normal flow of metabolism. One of the disorders he studied is known as OTC deficiency, short for ornithine transcarbamylase, a protein essential for pulling ammonia out of the bloodstream. Children with the deficiency may seem completely normal at birth, only to slip into a [coma](http://health.nytimes.com/health/guides/symptoms/consciousness-decreased/overview.html?inline=nyt-classifier) a few days later.

“It’s one of the scariest things you can imagine taking care of,” Dr. Horwich said. “You have to work really fast to get them under control and get them detoxified.”

He and his colleagues deciphered the gene for OTC and began to study how it worked. They learned that the protein must first be delivered to the mitochondria, a jellybean-shaped structure inside the cell.

To track this journey, Dr. Horwich and his colleagues inserted the OTC gene into yeast cells. They then created mutant forms of the yeast, hoping that some of them would disable genes that are crucial for the delivery of OTC.

Proteins are intricately folded molecules, but research by other scientists had shown that proteins could not slip into mitochondria in their fully folded shape. To pass through narrow entryways, they needed to unfold, Then, before they could begin to do their jobs, they had to fold up.

In 1987, Dr. Horwich and his colleagues began to wonder if the OTC protein might need help to fold — a notion that at the time, he said, was “heresy.”

A newly made protein starts out as a chain of amino acids. Their attraction and repulsion drives them into the protein’s final shape. In the 1950s, the American biochemist [Christian Anfinsen](http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1972/anfinsen-bio.html) unfolded proteins and put them in test tubes. He found that on their own, the proteins could fold into their proper shape. The experiment, which brought Dr. Anfinsen a Nobel Prize in 1972, led to a consensus that proteins can fold on their own.

Dr. Horwich and his colleagues thought Dr. Anfinsen might not have gotten the whole story. Other scientists have found so-called heat shock proteins that can cradle other proteins that have misfolded. Perhaps, Dr. Horwich and his colleagues thought, proteins needed help folding when they formed under normal conditions, too.

To find out, Dr. Horwich and his colleagues sorted through the yeast. They eventually found a yeast strain that could deliver the OTC proteins into mitochondria but could not get them to work. It was possible that this mutant lacked the ability to fold the protein properly. Dr. Hartl, an expert on how proteins are imported into the mitochondria, got wind of Dr. Horwich’s experiments and asked for some of the yeast to inspect. He soon called back to say, heresy or not, that he agreed.

Dr. Horwich, Dr. Hartl and their colleagues discovered that the mutated gene produced a molecule called heat shock protein 60 (the 60 refers to its mass). Versions of this protein are found in all living things.

To find out how the protein worked required years of painstaking research. Collaborating with the scientist [Paul Sigler](http://opac.yale.edu/news/article.aspx?id=5476) of Yale, who died in 2000, Dr. Horwich made crystals of the protein to determine its structure. Then he and his colleagues ran experiments to test ideas about how the structure might let the protein do its job.

Dr. Horwich also continued working as a physician until he switched to the lab full-time in 2002. “I’d run to the wards, take care of my patients, and I’d go back to the lab and work on these basic things,” Dr. Horwich said.

HSP60, he found, folds proteins in an unexpected way. It does not grab a protein and fold it like an origami master. Instead, it gives the protein the isolation it needs to fold itself.

HSP60 resembles two barrels stuck end to end. An unfolded protein can get trapped in one of the barrels, whereupon a lid slams shut. Once sealed inside, the protein can begin to fold into its proper shape. The lid stays sealed for 10 seconds before popping open, allowing the protein to escape. A new unfolded protein can then drop into the other opening, and another lid traps it in turn. If a protein does not fold completely in its first visit to the changing room, it can fall back in again.

This discovery gave an unexpected twist to Dr. Anfinsen’s pioneering work. Proteins can indeed spontaneously fold into their proper shape in a test tube. But cells are not test tubes. “There are all sorts of chances for mishaps to occur,” Dr. Horwich said.

The heat inside an ordinary cell can cause proteins to jitter so much they will fold incorrectly. Cells are also crowded places, so a new protein may accidentally stick to another one instead of taking its proper shape. HSP60 provides a new protein with tranquil isolation from the cell’s chaos so that it can fold properly. In effect, HSP60 is the cell’s test tube.

As Dr. Horwich has investigated how proteins get folded, other researchers have found links between misfolding and a number of diseases. People with Alzheimer’s disease develop clumps of tangled proteins in their brains, for example. A number of scientists are exploring the possibility that by preventing misfolding, or refolding defective proteins, doctors might be able to treat these diseases.

Dr. Horwich is one those scientists. He is investigating whether it is possible to get cells to make extra copies of protein-folders like HSP60. The additional boxes might give proteins more of an opportunity to be set right.

But Dr. Horwich’s experience in the clinic keeps him from promising too much from his continuing research. “Going to the bedside is immediately humbling,” he said. “The hope is that we’ll get better and better at providing something for people who get sick.”