Acceptance speech

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Peter Walter, awardee in the Biology and Biomedicine category (16th edition)

In the early 1900s, the British mathematician Godfrey Hardy defined scientific beauty as an art form in which outstanding science gives you "cerebral chills and intellectual kicks" – and combines three qualities: significance, generality, and unexpectedness.

This year's BBVA Foundation Frontiers of Knowledge Award in Biology and Biomedicine beautifully resonates with Hardy's criteria. The discovery of Ulrich Hartl and Art Horwich that protein folding into the correct three-dimensional shapes is usually assisted by molecular chaperones was entirely unexpected because, at the time of their discovery, our thinking was dominated by the Nobel Prize-winning dogma of Christian Anfinsen, posing that a protein's shape is entirely specified in a protein's amino acid sequence. Hence, proper protein folding would need no further help. Yet chaperone-assisted protein folding proved to be generally true for thousands of proteins in all living cells, and its dysfunction connects to numerous human diseases significantly.

The same holds true for Kazutoshi Mori's and our work on the unfolded protein response. Nobody expected that proteins are recognized before they assume their final shapes by the dedicated molecular machinery we discovered. We discovered dedicated unfolded protein sensors that ascertain that enough chaperones can be made to help them fold correctly and efficiently. But, the unfolded protein response also evaluates the severity of imbalances, instructing the cell to die to avoid harm to the organism if protein quality cannot be maintained.

When we began working on the unfolded protein response, we found ourselves traveling along a road that seemed predictable and straight. But suddenly, the ground shifted, and we stepped into a morass, in which the seemingly familiar dots that gave us a sense of security no longer connected. Walking on, undeterred, we deciphered one of the most unusual cell-internal communication pathways. To top it off, the salient features of what we learned from simple, single-celled brewer's yeast held true for human cells. These features now emerge as impacting players in a plethora of devastating human diseases, including cancer, diabetes, and neurodegeneration, giving us hope that our esoteric findings can be translated into tangible benefits for humankind.

Biology, however, is not mathematics, nor is it physics, nor chemistry. As biologists, we are not free to impose our own axioms to inject beauty into our work. In our work, Nature presents our playing field, and it is our task to decipher the governing rules. Disconcertingly, Nature deploys the strategy of random walk, of mutation, and selection, leading to the evolution of the world that surrounds us. Nature then presents us with the most fascinating puzzles to decipher: the inherently unpredictable Rube Goldberg machines that make up a living cell.

The point here is that none of our discoveries were predictable. Neither one of us would claim to be a genius mathematician akin to Hardy or an artist who begins with an empty canvas and control over the elegance of their work. We are explorers who face the chaotic randomness of evolution. To me, diligently deciphering some of Nature's guarded mysteries has been a fascinating, all-consuming journey filled with adventure, cerebral chills, and intellectual kicks. Yes, this journey required radical thinking and fearless experimentation. But only in the end did it all combine — serendipitously — into a story of unexpectedness and, we hope, lasting significance.

Finally, I wish to thank the Foundation, the committee, and the nominators for bestowing this honor on us. Most importantly, the work that receives this recognition was performed by numerous outstanding graduate students and postdocs over the last 30 years. I am deeply indebted to their courage and trust, walking along with us on our intertwined and meandering paths of discovery, and accept this honor on behalf of all members of our teams, past and present.

Thank you — Gracias — Eskerrik asko.

A toast to discovery!