VNIVERSITAT DE VALÈNCIA

Honoris Causa Ceremony

***Lectio* / Speech**
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I feel very honored to be here today, and to be able to give this lecture as the most recent Honorary Doctor of the University of Valencia. It's a humbling thought that the UV has been around ever since 1499, while my own university–Stockholm University– was founded in 1877 and became a full university only in 1960. With such a meager history, the academic traditions of Stockholm University pale in comparison to those here in Valencia, and I felt that I needed to consult Wikipedia to prepare myself for this occasion. And Wikipedia told me some useful, or at least entertaining, facts about the honoris causa degree:

- The earliest honorary degree on record was awarded to Lionel Woodville in the late 1470s by the University of Oxford. He later became Bishop of Salisbury.

- The Rev. Theodore Hesburgh held the record for most honorary degrees, having been awarded 150 during his lifetime.

- The awarding of an honorary degree to political figures can prompt protests from faculty or students. In 1985, as a deliberate snub, the University of Oxford voted to refuse Margaret Thatcher an honorary degree in protest against her cuts in funding for higher education.

- Between the two extremes of honoring celebrities and formally assessing a portfolio of research, some universities use honorary degrees to recognize achievements of intellectual rigor.

From the long list of previous Honorary Doctors at UV, it appears that UV subscribes to the latter principle, and I feel that, as a newly minted Honorary Doctor, I'm in amazing company–it is indeed a very special experience to be here! To be honest, one aspect that makes it an extra-special experience is that this is the first– and most likely the last–time that I present a pre-written speech, reading from a script and with no slides or even a whiteboard as aids. This is quite a challenge, but an interesting one...

Turning now to science, my academic field is in the borderlands between biochemistry, biophysics and bioinformatics. I took my first uncertain steps into science as a PhD student in the mid-1970'ies, and quickly stumbled over a problem that has been with me ever since: how proteins get across–or sometimes integrate into– cellular membranes.

In hindsight, I count myself lucky that I did my PhD in a theoretical physics department, with a supervisor who adhered to the typical dictum of the theoretical physicist: PhD students should be left alone to find their own scientific problems to study, not told what to do. In today's university environments this of course would be madness–how can you expect students to finish a PhD in 3 or 4 years if they're not

given a project on day one–but I was too naïve to understand this, and happily goofed around until a good problem presented itself. Which, fortunately, it did before too many years had passed by. And, to be honest, there is nothing quite like finding your own problem to work on to boost your self-confidence!

How proteins get across membranes may sound like a typical academic research problem, with little real-world relevance. And to some extend it is: every cell in our body can export proteins into the bloodstream and we would simply like to know how this is possible, how the molecular mechanisms behind protein export works. We're just curious. But the problem also has medical and pharmaceutical relevance, since failure to export certain proteins can lead to disease.

The giant in this particular filed of science was Günter Blobel at the Rockefeller University in New York, who passed away in 2018. Already in 1971, together with David Sabatini, he proposed the so-called signal hypothesis, and in 1975 showed biochemically that proteins destined for export from the cell are made with an extra extension–a signal peptide–that serves as an address label to route them into the export pathway. I began as a PhD student in 1975, and so had the good fortune to start working in what was really virgin territory at the time. In fact, during my very first trip to the US in 1979, I was lucky enough to be invited to a meeting at Cold Spring Harbor outside New York organized by Blobel and Sabatini, where all the early pioneers in the field got together–an amazing experience for a young PhD student!

Now let me fast-forward to 2019, and ask what we–all the scientists across the world that became interested in protein export–have learned about the process in the 45 years that have passed since Blobel took the first steps. And what this tells us about how science progresses.

Well, on one level you can say: what we've learned is simply that Blobel's speculative signal hypothesis was essentially correct–end of story. But on another level, you can say that a lot of deep thinking by a lot of very clever people taking advantage of the ever more sophisticated technical tools available to science, has uncovered some beautifully simple mechanistic principles and some amazingly advanced cellular machinery for protein export. Central to the export mechanism are two players: the ribosome–the machine that makes all the proteins in the cell and arguably is the most complex of the molecular machines that underpin life–and the so-called translocon–a channel protein through which newly synthesized proteins can be threaded from the inside of the cell to its outside. To state it briefly: we now know that the signal peptide on an exported protein guides the ribosome to the translocon, such that the protein can be threaded through the translocon channel as it is being synthesized by the ribosome.

Today, we also know how these same components–the ribosome and the translocon– cooperate to make membrane proteins, i.e., proteins that are integrated

into the cell membrane itself, rather than be exported across it. Membrane proteins are particularly important in biochemistry, because they help transport nutrients, metabolites, and ion across cellular membranes, and further mediate a plethora of signaling events that coordinate the actions of the different organs in the body. Because they serve as gatekeepers between the cell and its surroundings, membrane proteins are prime drug targets, and more than 50% of all drugs currently on the market target membrane proteins.

In our own research we have tried, and are still trying, to work out the basic mechanisms of how the cell manages to insert membrane proteins into its various membranes. The main problem faced by the cell in this instance is that membrane proteins–being designed by Nature to fit nicely into the membrane environment–will not be happy outside the membrane, but will misfold and aggregate if exposed to the aqueous cytoplasm. The solution, it turns, out, is as elegant as it is simple: target ribosomes that make membrane proteins to the same translocon channel used for exported proteins, and endow the translocon channel with a "lateral gate" that can open towards the surrounding membrane. In this way, the membrane protein can pass sideways from the channel, through the lateral gate, into the membrane, as it is being made on the ribosome. The protein is never exposed to the cytoplasm, and lives happily in the membrane forever after.

Thus, what we find is that exported proteins and membrane proteins, despite their very different chemical characteristics, are handled by the same cellular machineries and according to the same mechanistic principles. Principles that we now have a good grasp of, even if many details still remain to be worked out.

Looking back over these 45 years, what was no more than a simple hand-penciled sketch on a piece of paper in 1971 has been transformed into a detailed mechanistic description of a central biochemical process, complete with atomic-resolution three-dimensional structures of all the components involved. The ribosome itself is a behemoth that contains some 220.000 non-hydrogen atoms, the translocon is much smaller but resisted all attempts to determine its structure until 2004, and other components discovered during the 1980'ies and 90'ies add additional complexity. The history of the field is a beautiful illustration of how an early breakthrough by one or a few researchers excites a wider scientific community and eventually results in deep insights into Nature's hidden ways. Simply said: science in action, when at is best.

But our story also has other dimensions, that are characteristic of how science has developed over the past several decades: the increasing pressure to "win the race" and publish in the best journals, the increasing competition for academic positions and grants, the increasing focus on "excellence" with the best & biggest groups getting the lion's share of the resources–"To those that have, more will be given". These are all issues that spring from the fact that science has gone global, that nations see science

as a way to compete for economic and political influence–or, simply put, that modern science costs a lot of money.

Yet, as scientists we must not lose track of what made us choose this particular career in the first place: our curiosity, our drive to pose questions and find answers, the satisfaction we get from teaching and interacting with students, the fun of a good collaboration. And to fight as best we can in our everyday life to preserve the best aspects of the academic traditions: honest intellectual exchange, scientific rigor, a spirit of collegiality, the kind of work environment that makes you feel that Monday is the best day of the week. To the extent that Honorary Doctorates help perpetuate such values–and I believe they do–let's try our best to uphold this great tradition. As does the University of Valencia, and also, in an admittedly less grand way, does Stockholm University. Thank you very much!

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