Investidura com a Doctor "Honoris Causa" per la Universitat de València a Kurt Wüthrich

Discurs d'acceptació

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Lectio by Kurt Wüthrich on the occasion of the Investiture as Doctor 'Honoris Causa' by the Universitat de València, 14th of June, 2004

Excelentisimo y Magnifico Rector,
Excelentisimas y Ilustrisimas Autoridades,

Very Honorable Rector Magnificus,
Very Distinguished Guests,

Let me express my heartfelt thanks for the invitation to join you today in the unique surroundings provided by the University of Valencia. I consider it a very special honor to receive an academic degree from this old and very distinguished school. I only regret that I have to deliver this address in English. I admire the Spanish language for the outstanding culture that it represents as well as for its global importance, but unfortunately I have not become as familiar with it as I would have liked. Fortunately, the present visit in Valencia provides an opportunity to add a few new words to my limited Spanish vocabulary.

I assume that you are interested to hear about my research projects. My principal scientific interest is to use nuclear magnetic resonance (NMR) spectroscopy for studies of structure and function of biological macromolecules, such as proteins, nucleic acids, lipids and carbohydrates. My research group at the Eidgenössische Technische Hochschule (ETH) in Zürich, Switzerland, pursues several structural biology projects with the use of NMR spectroscopy, among which investigations of prion proteins have recently attracted special interest. Prion proteins have an important role in the pathology of transmissible spongiform encephalopathies (TSE), such as mad cow disease, scrapie in sheep, and Creutzfeldt-Jakob disease (CJD) in humans. My second scientific team at The Scripps Research Institute (TSRI) in La Jolla, California, USA, is focused primarily on exploring the use of NMR techniques in the newly emerging field of structural genomics. There are many additional areas of NMR applications in biological and biomedical research as well as in medical diagnosis, and I am glad to know that important activities in the use of NMR techniques are pursued here at the University of Valencia.

In structural biology, NMR spectroscopy is unique among the methods available for three-dimensional structure determination, since the NMR data can be recorded in solution. Considering that body fluids such as blood, stomach liquid and saliva are protein solutions where these molecules perform their physiological functions, knowledge of the molecular structures in solution is highly relevant. In the NMR experiments, solution conditions such as the temperature, pH and salt concentration can be adjusted so as to closely mimic physiological fluids in living organisms. Conversely, the solution conditions may also be changed to quite extreme non-physiological conditions, for example, for studies of protein denaturation. In addition to three-dimensional structure determination, NMR applications include investigations of dynamic features of the molecular structures, as well as studies of structural, thermodynamic and kinetic aspects of interactions between proteins and other macromolecules or low molecular weight ligands. Again, for these supplementary data it is of keen interest that they can be measured directly in solution.

In our work during the last two decades we encountered several molecular systems where the advantage of structural studies in solution is readily apparent. A first example is the *Antennapedia* homeodomain, where the polypeptide chain is only partially folded, with both chain ends showing pronounced disorder. However, in the complex of the homeodomain with its operator DNA, which is formed during the process of differentiation in higher organisms, the N-terminal chain end is located in the minor groove of the DNA where it adopts a well-defined structure. This mode of intermolecular recognition by a flexibly disordered polypeptide tail illustrates the functional importance of proteins containing partially or fully unstructured polypeptide segments, which will then become uniquely structured upon binding of the protein to its physiological reaction partners. A second example are mammalian prion proteins, for which the three-dimensional structure of the benign "cellular" form includes a flexibly disordered 100-residue tail linked to the N-terminal end of a globular domain. Considering that the mechanism of transformation of the cellular prion protein into the aggregated, disease-related form is still subject to speculation, the observation of this outstandingly long flexible tail has been highly intriguing. By now, work in many research groups around the world has identified a large number of proteins that are partially or fully unstructured, among which many have important roles in the regulation of nucleic acid functions.

The impact of NMR in structural biology has to be evaluated in the frame of reference presented by the other major technique in this field, X-ray diffraction with single crystals. Crystallography is the most efficient technique for structure determination, with about 20'000 crystal structures in the Protein Data Bank, as compared to about 5'000 NMR solution structures. Crystallography has also proven its ability to determine very large structures, including intact viruses. On the other hand, partially folded polypeptide chains are usually difficult to crystallize. Furthermore, if crystals can be obtained, the chain segments that are disordered in solution will either be ordered by intermolecular contacts in the crystal lattice, or they will not be visible by X-ray diffraction. As a consequence, NMR has in many cases been the only method capable of providing structural information on partially folded polypeptides, and the concept of functional disorder in proteins is intimately linked with the use of NMR. Although a standard protocol for NMR structure determination provides a static picture of the structured as well as the unstructured chain segments, additional NMR experiments can provide information on the rate processes that mediate transitions between discrete conformational states and thus supplement the static structure with data on the dynamics of the protein.

Overall, NMR characterization can include structure determination, description of interactions with other molecules, as well as data on dynamic properties, which makes NMR spectroscopy with biological macromolecules an intellectually most stimulating occupation.

After this brief account on my current professional activities, I would like to add a few words about my background and my life as a scientist. During my childhood I lived in the small town of Lyss in the Swiss canton of Bern, which was at the time a rural area of farmland, forests and rivers. My interests during childhood were largely influenced by our living in an old farmhouse, where my family produced a wide range of farming goods. The resulting intense contacts with plants and animals awakened my interest in natural science at an early age. I enjoyed all aspects of work and fun with a private trout river, and as a boy I had set my mind on becoming a forest engineer. These early experiences have left a lasting impression; I still like to go fishing, and I consider it a privilege to tend our family forest.

During my high school years in the bilingual Swiss city of Biel/Bienne a new important element came into my life. The Gymnasium Biel was informally attached to the Swiss Federal School of Sports and Gymnastics in nearby Magglingen, and thus my interest in competitive sports was awakened. Sports have then had an important role in my life up to the present days. I not only obtained the "Eidgenössisches Turn- und Sportlehrerdiplom" as one of my University degrees, but for many years I also played in a competitive soccer league. I am thus well prepared to appreciate the outstanding performances of the FC Valencia and the UD Levante in the 2003/04 season. However, in spite of extensive sports activities, natural science has been a lot of fun during all these years. To combine the two, I envisaged a career as a high school teacher with a heavy involvement in sports. For most of the duration of my University studies in natural sciences I therefore held jobs as a part-time instructor of physics, chemistry and gymnastics in high schools, and as a ski instructor in Swiss mountain resorts.

Formally, this life style came to an end at the age of twenty-five, when I obtained my Ph.D. degree at the University of Basel in Switzerland and moved to the USA for postdoctoral training. However, I remember that physical exercise continued to take up a large part of our time also in the USA. Looking back, I actually do not remember that I ever knowingly took a decision to leave sports for full-time work in scientific research. It was much more so that I had the good fortune of getting associated with three of the most outstanding research centers of the 1960s. This started with postdoctoral training at the University of California in Berkeley, which was followed first by employment as a research scientist with Bell Telephone Laboratories in Murray Hill, NJ, USA, and then by a faculty position at the ETH Zürich in Switzerland. As I was quite successful with my work in these distinguished institutions, it was an automatic process that my time got more and more devoted to my research projects. Thereby I may also have transferred some competitive spirit from the football field to my research teams. This competitive edge is nicely illustrated by the long-standing race to obtain NMR spectra of ever bigger molecular structures, our current "record" being at a molecular weight of 870'000.

Considering my background, it seems quite natural that I would place importance on transfer of our results into practical applications. For example, NMR structure determination of proteins, and structural biology quite generally, provides a foundation for rational drug design in the biomedical sciences. There is also a broad range of NMR applications in medical diagnosis. The close relations between basic NMR research and a wide range of practical applications led to collaborations and consulting with industrial enterprises, which has been an important and in many ways also particularly satisfactory part of my professional life.

I would like to end my presentation with a comment about the role of academic distinctions in the life of a scientist. This role is perhaps best appreciated by a comparison of rewards in sports competition and in basic science. Scoring a goal during a football game, winning a football game, or even winning a championship draws immediate applause and plenty of media attention. In contrast, important breakthroughs in basic science are often met with disbelief and criticism, and many years may go by before a new discovery is accepted by the scientific community. It can take more moral strength to live through such periods of success without broad acceptance than through years without significant advances in one's projects. The award of academic distinctions has an important role in providing encouragement and support in struggles for acceptance of important new insights. In this sense I would like to express again my gratitude to the University of Vanència for the high distinction bestowed upon me today, and to all of you for having joined the festive ceremony.