Protease control in Health and Disease and my Experience with its Translation into Practice and Business

Professor Dr Robert Huber

Max-Planck-Institut fuer Biochemie
Emeritusgruppe Strukturforschung
D-82152 Martinsried – Germany;
Technische Universität München, TUM Emeritus of Excellence
D-85747 Garching, Germany;
Universität Duisburg-Essen, Zentrum für Medizinische Biotechnologie
D-45117 Essen, Germany;
Cardiff University, School of Biosciences
Cardiff CF10 3US, UK

Summary

As a student in the early nineteen sixties, I had the privilege to attend winter seminars organized by my mentor, W. Hoppe, and by M. Perutz, which took place in a small guesthouse in the Bavarian-Austrian Alps. The entire community of a handful of protein crystallographers assembled in a room which served as living and dining room and as auditorium for the lectures.

Today structural biologists organize large congresses with thousands of attendants and there exist many hundreds of laboratories specialized in this field. It appears to dominate biology and biochemistry very visibly if we count covers in scientific journals displaying macromolecular structures.

Structural biology was successful, because it was recognized that understanding biological phenomena at the molecular and atomic level requires to see those molecules.

Structural biology revealed the structure of genes and their basic mechanism of regulation, the mechanism of enzymes' function, the structural basis of immune diversity, the mechanisms of energy production in cells by photosynthesis and its conversion into energy- rich chemical compounds and organic material, the mechanism that makes muscle work, the architecture of viruses and multi-enzyme complexes, and many more.

New methods had an essential impact on the development of structural biology. Methods seemed to become available in cadence with the growing complexity of the problems and newly discovered methods brought biological problems within reach for researchers, a co-evolutionary process of the development of methods and answerable problems.

An important additional incentive for structural biology came from its potential application for drug design and development by the use of knowledge of drug receptors at the atomic level. The commercial interest in application spurred this direction of research enormously.

My lecture will start out with a very brief review of the history of protein crystallography and continue with our studies since 1970 on proteolytic enzymes and their control. Proteolytic enzymes catalyse a very simple chemical reaction, the hydrolytic cleavage of a peptide bond. Nevertheless they constitute a most diverse and numerous lineage of proteins. The reason lies in their role as components of

many regulatory physiological cascades in all organisms. To serve this purpose and to avoid unwanted destructive action, proteolytic activity must be strictly controlled. Control is based on different mechanisms which I will discuss and illustrate with examples of systems and structures determined in my laboratory:

a) by specific inhibition with natural and synthetic inhibitors
b) by enzymatic specificity
c) by activation from inactive precursors accompanied or not by allosteric changes
d) by co-localization of enzyme and substrate
e) by cofactor binding accompanied or not by allosteric changes
f) by controlled access to the proteolytic site.

The regulatory principles offer new opportunities of intervention for therapeutic purposes and use in crop science.

I then will let you share my experience with the foundation and development of two biotech companies with different business models, but both based on basic academic research in
structural biology:
Proteros (**www.Proteros.com**) offers enabling technology services for Pharma- and Crop science companies imbedding all steps of the workflow molecular and structural biology can provide and commands and uses its platform for the generation of leads from identified targets to in vivo Proof of Concept (PoC).
Suppremol (**www.Suppremol.com**) specializes in the development of novel immunoregulatory therapeutics for the treatment of autoimmune diseases on the basis a recombinant, soluble, non-glycosylated version of the human Fcγ receptor IIB.