UNIVERSITÀ
DI PARMA

Conferimento del titolo di

Dottore Magistrale ad honorem in

Chimica e Tecnologia Farmaceutiche *a*
William Allen Eaton

Laudatio

Prof. Andrea Mozzarelli

Professore ordinario di Biochimica

Parma, Aula Magna

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Rector, Colleagues, Ladies and Gentlemen,

It is a great honor and pleasure for me to deliver the Laudatio for William A. Eaton on the occasion of his Laurea Honoris Causa in Pharmaceutical Chemistry and Technology, granted by the University of Parma on behalf of the Italian Ministry of Education, University and Research. Dr Eaton is a truly outstanding scientist, recognized worldwide for his many pioneering research contributions to protein science. Dr Eaton's research goal throughout his life has been the understanding of protein function, dynamics and aggregation at a fundamental level. This has been achieved by investigating the biophysics and physical chemistry of hemoglobin function and regulation, the fundamental principles of protein folding, and the discovery of drugs for sickle cell disease, the latter being the subject of his Laurea thesis. His research journey started almost 60 years ago

Dr Eaton obtained his B.A. with Honors in Chemistry from the University of Pennsylvania in 1959. He was the first Willy Brandt - University of Pennsylvania exchange student with the Free University Berlin, Germany studying biophysics, in 1959-1960. He obtained the Doctor of Medicine degree from the University of Pennsylvania, School of Medicine, in 1964. Following his interest in proteins, he spent a summer period in 1962 working on protein biosynthesis supervised by Sydney Brenner at the Medical Research Council Laboratory of Molecular Biology, Cambridge, England, where many past and future Nobel prize winners, including Brenner, Crick, Perutz, Kendrew, Sanger were working at that time. Following graduation from medical school pursued a Ph.D. in Molecular Biology, at the University of Pennsylvania, completing his thesis in 1967 on "Single Crystal Spectra of Ferricytochrome *c* and Ferrimyoglobin Complexes in Polarized Light", under the supervision of the legendary spectroscopist Robin M. Hochstrasser, a great teacher, scientist and friend. Receiving both MD and PhD degrees was quite unusual in the 1960's, but allowed Eaton to have

a deep insights on both biomedical and biophysical problems and to address complex medical and pharmaceutical challenges with rigorous biochemical and physical approaches.

Because of the physician draft during Vietnam war Eaton was drafted as a medical officer into the US Public Health Service to fulfill his military obligation, He was fortunate to land a position at the National Institutes of Health, Bethesda, in 1968, and has been at the NIH ever since, apart from one semester teaching physical chemistry as a Visiting Professor at Harvard University in 1976 . He has been a member of the Permanent Scientific Staff of Laboratory of Chemical Physics at the National Institute of National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) since 1972, Chief of Laboratory of Chemical Physics since 1986, Scientific Director of the Intramural AIDS Targeted Antiviral Program of the Office of the Director since 1986, and was appointed NIH Distinguished Investigator in 2007.

Bill has received many honors and awards, including the election to the American Academy of Arts and Sciences in 1997, election to the National Academy of Sciences of USA in 2006, election to the Accademia Nazionale dei Lincei, as a foreign member in 2011, recipient of the Founders Award of the US Biophysical Society in 2006, the Hans Neurath Award of the Protein Society in 2009, Humboldt Research Award for Senior Scientists in 2009, the John Scott Medal of the City of Philadelphia in 2010, the Max Delbruck Prize in Biological Physics of the American Physical Society in 2011, and an Honorary Doctorate in Physics from the Free University of Berlin, Germany in 2016 with a Symposium in his honor on "Protein Folding Kinetics".

As Chief of the Laboratory of Chemical Physics, he is administratively responsible for 50 Ph.D. scientists and 10 technical staff, and as Scientific Director of the Intramural AIDS Targeted Antiviral Program, he is responsible for $6,500,000 per year budget distributed among 30-40 principal investigators working in the area of molecular, cell,

and structural biology of AIDS. The Laboratory of Chemical Physics, built by Dr. Eaton, is widely considered as one of the very top research laboratories in the world in the area of molecular biophysics and structural biology, with luminaries whom he hired that include the NMR spectroscopists Ad Bax and Marius Clore, and the theoretical chemist, Attila Szabo, all members of the National Academy of Sciences.

Eaton has been in great demand to present his work around the world having delivered over 230 lectures at scientific meetings and over 200 seminars at universities, including 15 at the University of Parma.

Eaton has published 165 papers, which is not considered many. But these papers have been very influential in the scientific community, as evidenced by the fact that 40 of his papers have been cited over 200 times, with a total 23,000 citations and an h-index of 82.

The PhD thesis studies of Dr. Eaton were focused on the determination of heme electronic transition dipole moment directions in myoglobin and cytochrome c using single crystal polarized absorption microspectrophotometry, a technique that was also applied at the University of Parma by Gian Luigi Rossi and coworkers for enzymes to compare protein structure and function in crystal and solution This technique is still one of the main activities of our biochemistry laboratory at the Department of Food and Drug. When Dr Eaton moved to the NIH in 1968, he continued his spectroscopic studies of single crystals, primarily on hemoglobin. He began his work on sickle cell hemoglobin in 1972 with the determination of the orientation of the hemoglobin molecule in the sickle hemoglobin fiber, which was an important piece of information for constructing a model for the fiber based on the sickle hemoglobin crystal structure. This study was followed by his truly pioneering equilibrium and kinetic studies with post-doctoral fellow, James Hofrichter, on the polymerization of sickle hemoglobin to form fibers that are the root cause of the pathology of the disease. The fibers make

the red cells less flexible, resulting in the possibility of occlusion of the small tissues of almost every organ in the body. In this work he and Hofrichter discovered the highly unusual kinetics of polymerization with a marked delay period prior to fiber formation that is enormously sensitive to the intracellular hemoglobin concentration. It is this delay that allows most cells to escape the smallest vessels tissues before fibers form and makes the disease survivable. His concept that disease severity is determined by the relation between the delay time and the transit time through the smallest vessels synthesizes an enormous amount of clinical data and revolutionized our understanding of the pathophysiology of sickle cell disease. Moreover, his studies with James Hofrichter and another post-doctoral fellow, Frank Ferrone, resulted in their development of a novel double nucleation mechanism, which has been adopted by the Dobson/ Knowles Cambridge group as the mechanism for formation of the amyloid fibers of Alzheimer's disease. I was fortunate to work with Bill at NIH in the 1980's to show that most cells escape the small vessels before sickling that resulted in an influential paper in the journal Science in 1987.

Bill took a 25 year break from sickle cell research in the early 1990's to focus primarily on the understanding how protein folds, where he has become a leader in the field by using lasers to enormously increase the time resolution in kinetic studies on both bulk and single molecule experiments. In addition to his protein folding work, during this period, Dr. Eaton began an important and fruitful collaboration with me and my colleagues at the University that continues today. Our collaborative work, which began with a paper in the journal Nature with Claudio Rivetti and Gian Luigi Rossi, settled a long-standing controversy by showing that oxygen binding to single crystals of the hemoglobin T quaternary structure is non-cooperative, as predicted by the famous quaternary two-state allosteric model of Monod, Wyman and Changeux. This work also led to the development and validation of a novel model for hemoglobin function, the Tertiary Two State model, which extends the model of Monod, Wyman,

and Changeux to include tertiary conformation changes. The model resulted from an extensive series of oxygen binding measurements on hemoglobin crystals and wet porous silica gels, carried out by Claudio Rivetti, Stefano Bettati, Stefano Bruno and Luca Ronda. These experiments were combined with detailed kinetic studies in solution and in silica gels carried out by Cristiano Viappiani and Stefania Abbruzzetti. During this collaboration Eaton visited Parma 2-3 times per year. In 2008, on the occasion of a symposium in Parma to honor his 70th birthday, he received a silver medal from the University of Parma and an award from Parma municipality.

In the last few years Dr. Eaton has returned to sickle cell research with the aim of discovering a drug that could be used to treat the millions of sickle cell patients in third world countries who will not have access to any of the curative hi-tech methods such as current stem cell transplantation or future methods such as gene editing. He has developed sensitive kinetic assays on intact red cells to test compounds for their potential therapeutic effect on sickle cell disease. His assay uses laser photolysis of the sickle hemoglobin carbon monoxide complex to rapidly create deoxyhemoglobin to induce sickling and an automated image analysis to detect the formation of sickle fibers in individual red cells. As a strategy for the most rapid path to bringing a drug to market, the first phase of the screen is being carried out on all U.S. Food and Drug Administration-approved and foreign approved drugs, as well as a much larger number of compounds that did not become drugs, but have been tested in clinical trials in humans. The success of this approach up to now is described in detail in his Laurea thesis and will be presented in his lecture.

The work that Dr. Eaton has carried out on hemoglobin S polymerization, as well as his work on fundamental aspects of protein folding, because of its importance for understanding protein misfolding, has turned out to be quite relevant to understanding the mechanism of peptide and protein aggregation that causes many

human diseases, such as Alzheimer's disease and Parkinson's disease. Eaton's research has always been closely connected to theory and he has always tried to develop and apply the simplest theoretical model to interpret his experimental results in order to expose the basic underlying biophysics of the system. His experimental results and theoretical modeling are providing critical benchmarks for the construction of a detailed picture of the sequence of events as a protein forms its native conformation from the random structures of the unfolded polypeptide chain. As a result, basic science turns to be applied science opening new avenues for the identification of novel therapeutic strategies.

In summary, William Eaton possesses a special expertise for designing and executing insightful experiments for understanding complex biological events. Moreover, he has the capability of describing molecular processes through a chemical-physics formalism that allows him to build models and from models make predictions that, in turn, generate other experiments in an almost endless series of ideas, experiments, challenges, and results that provide new and deep insights. After exhausting his coworkers, his papers are rigorous, dense, and innovative. However, postdocs that have worked in his lab have learned how to address difficult biological issues in a rigorous way. Therefore, Dr. Eaton is not only an outstanding scientist but also a great teacher that always pushes the limits of experiments and instrumentation, and, frequently, beyond that result in both instrumental and conceptual innovation. Eaton's science is never trivial or repetitive. His science is by definition the exploration of unknown biological systems and molecular events. I am grateful to him for teaching me how to be a researcher and, today, I am very glad that he is receiving the honor of Doctor in Pharmaceutical Chemistry and Technology from the University of Parma. One last and key feature of Dr. Eaton is his tremendous enthusiasm for research. I am fully confident that he will continue with major scientific achievements well after his 80th birthday that will occur next week. I hope that we will meet again here to

celebrate his 90th in the same way as we have celebrated his 70th birthday with a terrific scientific meeting at the University of Parma and we are celebrating his Laurea Honoris Causa this afternoon with a workshop on Protein Science in Human Disease with talks by outstanding scientists to which all of you are invited. Science is for life and William Eaton's life has been and is for science.

Prof. Andrea Mozzarelli

Parma, 25 maggio 2018