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COMMENTARY

# Reflections on professor Sir Christopher M. Dobson (1949–2019)

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**Abstract**
I have been invited to summarize my career with an emphasis on the time I spent in the laboratory of Prof Christopher M. Dobson, who sadly passed away on September 8th 2019, and to describe his role as a mentor. I accepted this slightly unusual request as it constitutes a unique way for me to express my deep gratitude and admiration for Chris.

## Early life in France and post-graduate study in Japan

After graduating from my local high school in 1988 in the southeast of France (Romans sur Isère), I spent 2 years of study gaining a technical diploma in Biochemistry from Grenoble (Lycée Louise Michel, 1988–1990) before being admitted to the Ecole Nationale Supérieure des Industries Agroalimentaires (ENSIA, Massy, France) where I trained as an industrial engineer in food science (1991–1994). During this time, I became interested in the use of high hydrostatic pressure as an alternative technique to heat treatment for sanitizing and texturizing food whilst better preserving its nutritive value, original colour and flavour. This method of food processing was pioneered in the mid-1980s by Prof. Rikimaru Hayashi (Head of Biomacromolecular Chemistry in the Department of Life Sciences at the University of Kyoto, Japan) and it was viewed as an extremely promising one by many European food companies and research groups. After working for a couple of years as a high school biology teacher, I earned a Monbusho scholarship to carry out a DSc in the Hayashi group in Japan (1996–1999). My studies initially focused on the textural properties of gels generated upon subjecting proteins to high hydrostatic pressure and low temperatures. After 1 year, I accumulated enough data to publish a paper on that project. I then decided to shift to a more fundamental topic, and I dedicated the final part of my PhD studies to analysing the mechanism of pressure-induced cold denaturation of carboxypeptidase Y, a protease from yeast (also discovered by R. Hayashi). This new orientation was determinant for my career, and without it, I most likely would never have met Chris! I enjoyed my DSc research with Hayashi-sensei; he was a very inspirational and motivational supervisor. He always encouraged his students to participate in international meetings and visit laboratories abroad to learn new techniques. I thus spent a few weeks in the laboratory of Prof. Claude Balny at INSERM in Montpellier (France) and in the laboratory of Prof. Patrick Masson at Centre de Recherches du Service de Santé des Armées (La tronche, France) in order to carry out stopped-flow and electrophoresis experiments under high pressure, respectively. With strong encouragement from Prof. Hayashi, I published seven papers during my DSc including two review articles and three conference proceedings (e.g. Dumoulin et al. 1998; Dumoulin and Hayashi 1998). Hayashi sensei was also keen to introduce his students to many aspects of Japanese culture such as Noh theatres, the local famous onsen (hot natural baths) and traditional restaurants. I retain great memories of these moments.

## A postdoctoral fellowship in Belgium

After Japan, I moved to the University of Liège (Belgium) to carry out postdoctoral work in the group of Dr. André Matagne, himself a former postdoctoral fellow of Chris Dobson 1993–1995, at the Center of Protein Engineering (CIP). My 2-year position was funded by a European biotechnology network aimed at investigating the stability and folding properties of a set of VHHs. VHHs are the antigen binding domains of the so called camelid heavy-chains antibodies (HcAb) which are devoid of light chains. HcAb had been discovered in the group of

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R. Hammers at the Vrije Universiteit Brussel (VUB, Belgiun) a few years earlier (Hamers-Casterman et al. 1993). This network involved Prof. Lode Wyns and Prof. Serge Muyldermans from the VUB who had generated VHHs against a range of proteins including human lysozyme. Of interest to this story is that the collaborating parties also included the group of Chris Dobson, who was at that time leading the Oxford Center for Molecular Sciences (OCMS). A few days after I came back from Japan, I visited Chris together with André; from this first meeting, I remember Chris's enthusiasm for the project, his great kindness and his humility.

During my 2 years in the group of André, we demonstrated the high conformational stability of VHHs (Dumoulin et al. 2002). No need to mention that I particularly appreciated the scientific environment of the CIP and the life in Liège since I decided to finally settle down there! Toward the end of my fellowship in Liège, I spent a few weeks in Oxford investigating how the binding of a VHH specific to human lysozyme (HuL) can affect the behaviour of lysozyme natural variants prone to forming amyloids. Within a few weeks, I collected a large amount of data showing that the binding of the VHH to a particular HuL amyloidogenic variant restores the structural cooperativity characteristic of the wild-type protein. These experiments benefitted from invaluable help provided by the following people; Prof. Carol Robinson and her PhD student, Alexander Last (analysis of H/D exchange profiles of mutant and wildtype HuL in the presence/absence of the VHH); Prof. Christina Redfield (mapping of the binding site of the VHH on the surface of HuL by NMR); and Dr. Denis Canet, a postdoctoral fellow in Chris group who first described the loss of global cooperativity of the amyloidogenic HuL variants (Canet et al. 2002). Up to that point, these few weeks were the most intense and memorable of my scientific life. Indeed, I will never forget the excitement of everyone (especially Chris) and the numerous meetings we had to discuss the results almost in real time. Back in Liège, I conducted further experiments, utilizing the complementary techniques of far UV-CD and tryptophan fluorescence, to further characterize the stabilizing effects of the binding of the VHH on the amyloidogenic variants of lysozyme. At the same time, Aline Desmyter and Klass Decanniere from Lode's laboratory solved the X-ray structure of the complex formed between HuL and the antibody fragment; that data combined with the NMR results allowed us to rationalize the effects of the VHH. However, one crucial piece of information was missing to make this into a great story: we did not know yet if the binding of the VHH antibody fragment inhibited the aggregation of the lysozyme variants into amyloid fibrils. This turned out to be a very challenging problem to solve experimentally since the VHH was not stable under the conditions known to trigger, in vitro, the aggregation of HuL variants into amyloid fibrils. To solve this problem, I moved to England to work full-time in the Dobson group.

## A research fellow at Oxford and then Cambridge University

At the end of my fellowship in Liège, I joined Chris's group at Oxford in the spring of 2001, initially with funding from a two-year Mary Curie Fellowship to work on the VHH/lysozyme problem described above. I arrived in Oxford just a few months before Chris moved to Cambridge University as the newly appointed John Humphrey Plummer Professor of Chemical and Structural Biology. After joining his group, it took me a year and half to find solution conditions where the variant lysozymes could form amyloid fibrils but at which the VHH was still functional and thus to be able to demonstrate the inhibitory power of the VHH on fibril formation (Dumoulin et al. 2003). During this time, Chris's attitude was very supportive, with a fine balance between gentle pressure, warm encouragements and liberal dollops of good humour. Chris had a unique ability to listen, motivate and encourage. I always felt enlightened, inspired and full of confidence during and after meetings with him. I would like to acknowledge the many valuable pieces of advice he gave me during this time, such as the importance of perseverance, hard work and being always positive.

Chris's interdepartmental appointment as a John Humphrey Plummer Professor of Chemical and Structural Biology was an opportunity for him to further develop his multidisciplinary approach to tackling problems – a trademark style that he was passionate about. He moved to Cambridge with a handful of postdoctoral fellows including Jesus Zurdo, Cait MacPhee, Mark Krebs and Michele Vendruscolo. We were quickly joined by Natàlia Carullà, John Christodoulou and Goran Larsson as new postdoctoral fellows and Caroline Wright and Kristen Lindorff-Larsen as PhD students. It took us about 4 months to fully set up the laboratory in the basement of the Department of Chemistry. When thinking back to this period, it was a unique and funny experience. Although Chris very rarely came down to the laboratory, he had a very clear and precise vision of how things were and should be going on there, especially with regard to the problems and the solutions required to overcome them. I remember one meeting that a few of us initiated, to discuss a list of issues related to the progress of installations within the lab. As soon as we entered his office, Chris very impressively went through all of our listed points and quickly provided helpful ways to overcome these difficulties. It was as if he had seen our list in advance! Over the next 2 years, we witnessed the arrival of nearly 50 talented PhD students and postdocs from all over the world and from a variety of disciplines. Chris established a unique intellectual and training environment that was supportive, stimulating, extremely creative and

sufficiently open-minded to allow each member to make the best of him/herself. He especially provided a great space for independent research by allowing each of us to choose the direction of our own research according to our specific interest while always providing illuminating guidance and support. It was also at this time (2002) that Chris started to work on proteins associated with neurodegenerative diseases, such as alpha-synuclein (Parkinson's disease) and the Aβ-peptide (Alzheimer's disease). Since that time, his research has had a tremendous impact in the field of medical research (Dobson 2017; Dobson et al. 2019). In 2012, he founded the Cambridge Centre for Misfolding Diseases which is currently based in the Chemistry of Health building at the Department of Chemistry at the University of Cambridge, and in 2016, he co-founded Wren Therapeutics, a biotechnology start-up company whose mission is to find new therapeutics for Alzheimer's disease. Chris received more than ninety academic awards and honours including the Royal Medal by the Royal Society "for his outstanding contributions to the understanding of the mechanisms of protein folding and misfolding, and the implications for disease" in 2009, and in 2014, he received both the Heineken Prize for Biochemistry and Biophysics and the Feltrinelli International Prize for Medicine. Last but not least, Chris was knighted in the 2018 Queen's Birthday Honours for his contributions to science and higher education.

Altogether, I spent 7 years in Chris' group (until 2008) including the last two 2 years during which I shared my time between Cambridge and Liège, supported by both Chris and a Belgian fellowship from the FRS-FNRS. Chris trusted his co-workers to take charge of projects and to work hard to make progress wherever they worked. He was very flexible and provided freedom to people to organize their work in relation to their personal situation, and he was a strong advocate of women in science. I had the great privilege to continue to work during these years investigating the mechanism of fibril formation by the amyloidogenic variants identified from patients suffering from lysozyme amyloidosis (Dumoulin et al. 2007). During this time, I had the chance to interact with numerous collaborators both within Chris's group (and in particular with Dr. J. R. Kumita) and also external to it. Lysozyme was a particularly special protein to Chris since he started working on it during his PhD. More than 150 of the > 800 papers he published during his career deal with lysozyme (mostly from either hen or human sources) including four published in Nature and three published in Science. I am proud to have contributed to this work on lysozyme, having published 22 of these papers together with Chris.

## A return to Belgium as permanent FRS-FNRS research associate

In 2008, I received a research associate FRS-FNRS position at the Centre of Protein Engineering (CIP) in the Department of Life Sciences at the University of Liège where I am still happily working today. In the first years, my interest was essentially focused on studying the aggregation properties of several proteins, including a series of model polyQ proteins (e.g. Scarafone et al. 2012; Huynen et al. 2015), as well as maintaining a strong interest in VHHs and HuL. During this time, I supervised five PhD students (Natacha Scarafone, Coralie Pain, Janice Dumont, Chloé Chavignon and Céline Huynen) and more than 25 Master students, including more than a dozen from the University of Padova through exchanges with Prof. Patrizia Polverino de Laureto to whom I was introduced by Chris for collaborative projects on HuL nearly 20 years ago (Frare et al. 2006). More recently, my research interests have broadened to encompass the generation and use of VHHs to tackle, via collaborative projects, a series of diseases. I am coordinating the DiaSyn EuroNanomedII project aiming at developing a PET imaging radiotracer for alpha-synuclein (aSyn) detection and quantification in the brain. This project involves: Dr. Mathieu Cinier (Affilogic, Nantes, France), Prof. A. Luxen (GIGA-CRC, ULiège), Dr. Anne Michel (UCB-Pharma, Braine l'Alleud, Belgium), Prof. Rosario Moratalla (CAJAL Institute, Madrid, Spain) and Dr. Maxime Culot (University of Artois, France). Moreover, in collaboration with the group of Dr. Pierre Lafaye (Institut Pasteur, Paris) and Prof. Alain Vanderplasschen (Fac. Veterinary Medicine, ULiège) we are developping VHHs against specific aSyn post-translational modifications as tools to better understand the role of these later on the aggregation process of aSyn. The second disease we are interested in is cystic fibrosis (CF). In patients affected with CF, chronic respiratory infections lead to the release of proteases whose actions contibute to the destruction of the lung tissue. Within an Interuniversity project leaded by Dr. Rita Vanbever (UCLouvain, Belgium) and involving Prof. Teresinha Leal (UCLouvain) and Prof. S. Muyldermans (VUB), we aim at developing a nanomedecine inhibiting such enzymes for the treatment of the respiratory pathology of CF. Moreover, in collaboration with Rita and Serge, we are developing VHHs offering a sustained presence of a drug protein within the lung to treat CF. We are also involved into a project leaded by Dr. Jo Caers (GIGA3I, ULiege) aiming at developing VHHs for the immunotreatment of multiple myeloma. Last but not least, we collaborate with the group of Prof. Moreno Galleni (CIP) to generate VHHs inhibiting a series of enzymes involved in antibiotic resistance, a research topic of particular importance at CIP. My group is presently constituted by two talented postdoctoral fellows, Dr. Rita Maalouf and Dr. Francisco Morales, an invaluable technician Mr. Joël Moray, and three

**Fig. 1** Professor Christopher Dobson with researchers involved in the I.A.P network working on VHHs and amyloidogenic proteins at the time of the 1-day symposiums on Protein Folding and Stability, organized by Prof. André Matagne in 2005. From left to right: André Matagne, Chris, Mireille Dumoulin, Jean-Marie Frère, Lode Wyns, Els Pardon, Katja Conrath and Erwin De Genst

motivated Master students, Michele De Sabato, Paola Redeghieri and Ludovica De Ceasaere.

**Fig. 2** Professor Christopher Dobson when he received his Honoris Causa degree from the University of Liège in 2007

After my departure from Cambridge, I continued to collaborate with Chris on the HuL topic. During that time, I regularly visited his group collaborating with Dr. Janet Kumita, Dr. Erwin de Genst, Dr. Xavier Salvatella and Dr. Alexander Buell (e.g. Buell et al. 2011; Mossuto et al. 2011; Kumita et al. 2012; Ahn et al. 2016). Moreover, for many years, Chris had a special link with the University of Liège and especially with André Matagne. Together with André and Lode, he was involved in a Belgian Interuniversity Attraction Poles (I.A.P., 2002–2007) during which the work on VHHs directed toward alpha-synuclein was initiated (De Genst et al. 2013). None of the work involving VHHs and amyloid fibril formation would have been possible without the close collaboration between the group of Chris, Lode and André, and I am lucky to have been part of such a productive network (Fig. 1). One of the lessons I learned from Chris, was the importance of local and international collaborations – advice that I am still following to this day (e.g. Vandevenne et al. 2007, Gustot et al. 2013; Pansieri et al. 2017; Cawez et al. 2018). Chris visited the University of Liège on many occasions. On two of these occasions (2005 & 2012), he gave a talk during the 1-day symposiums on Protein Folding and Stability, organized annually by Prof. André Matagne since 2002. In 2007, Chris received a Honoris Causa degree from the University of Liège (Fig. 2). At that occasion, he came along with his wife Mary, and we spent a couple of great days with the two of them. I would like to express my deep gratitude to Mary for all the kind attention she paid to me while I was working at, or visiting, Cambridge. Upon hearing the news of Chris's death, I was touched by several messages from people who had met him only once while he was visiting Liège, expressing their sadness and appreciation for Chris's great scientific contribution as well as his enormous kindness. This in itself provides a powerful testimony to Chris's uncanny ability to interact with people and to touch them in a unique way.

## Some final words of tribute to Professor Sir Christopher M. Dobson

Over all of the years I spent in his laboratory (and even after that), Chris taught me so many things that it is difficult to report them all here. In particular, he taught me in many different ways how to become an independent researcher and how to perform good science. These lessons have been extremely important in shaping my career. Chris had an exceptional talent in writing; his numerous corrections of my manuscripts provided a unique way to learn how to make the most of data, how to put it in perspective and how to correctly frame it within a larger context. Perhaps, most importantly, he taught me, and many others, how to write a good paper. Chris gave me the opportunity to actively participate in the writing of

grant applications which culminated in my management of the work package that Chris was in charge of within a large European network project . When I obtained my position in Liège, Chris worked for my inclusion in this network as an independent PI; this is an example of his generosity and devotion to help establishing young researchers. This turned out to be an extremely valuable learning experience for the future of my career. It also gave me the opportunity to supervise Masters and PhD students. His advice on how to perform these duties remains invaluable to this very day.

Chris was a precious pillar of support and an incomparable source of inspiration for all the scientists and students he interacted with. He will be sorely missed, and his legacy will live through the work of each of who had the chance to work with him. Being mentored by such a great scientist and a passionate man, committed in a unique way to the people he worked with, has been one of my greatest privileges, and I will cherish every moment and discussion I shared with him.

Thanks for all Chris! You will be for ever in my mind and heart.

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