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EDITORIAL

Dr. Alexander Wlodawer—celebrating five decades of service to the structural biology community

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This 75th birthday tribute to our Editorial Board member Alexander Wlodawer recounts his decades-long service to the community of structural biology researchers. His former and current colleagues tell the story of his upbringing and education, followed by an account of his dedication to quality and rigor in crystallography and structural science. *The FEBS Journal* Editor-in-Chief Seamus Martin further highlights Alex's outstanding contributions to the journal's success over many years.

July 2, 2021, will be a special day for Alexander Wlodawer, all of his friends, and numerous mentees, associates, and collaborators. In this 75th Birthday tribute, we want to celebrate his outstanding scientific career and unusual personality. Alex's intellectual abilities are several standard deviations above average, and his interactions with collaborators, both senior and junior, are examples of how to be demanding and strict but gentle and friendly at the same time. Alex is currently affiliated with the Structural Biology Program of the NCI at Frederick and serves on several scientific committees and boards, including a long period of service on the editorial board of The FEBS Journal.

Alex was born just after World War II in Frankenstein, which is now known as Zabkowice Slaskie in Poland. The town's name is related to a modern-day Prometheus, who stole fire from the gods and gave it to humanity. Even as a small child, he was not the typical character. Most children in the early 1950s wanted to be firemen, soldiers, or airplane pilots. At the age of 4, Alex was a frequent visitor in his mother's laboratory (Paulina Wlodawer, one of the most eminent biochemists in Poland). When asked by Prof. Niemierko, the Director of the Institute (of Experimental Biology, better known as the Nencki Institute in Warsaw), 'What would you like to be?' Alex famously replied with resolute confidence—'A scientist'. Fourteen years later, he became a student of physics at the University of Warsaw.

When in high school, Alex was selected to become a member of the Polish delegation attending a meeting of the American Junior Red Cross on the Centennial

Abbreviations
ALL, acute lymphoblastic leukemia; IUCr, International Union of Crystallography; PDB, Protein Data Bank.

Anniversary of the Red Cross in the United States. That meeting in the summer of 1962, with a visit to the White House hosted by President John F. Kennedy (Fig. 1), has inspired and truly changed the life path not only of Alex Wlodawer, but also the lives of many of the 100 delegates. One of them was Ban Ki-moon, who later became United Nations Secretary General. The friendship with the Secretary General of the UN helped during the organization of the UNESCO International Year of Crystallography in 2014.

As a High School junior, Alex won the Chemistry Olympiad, which gave him free admission to any university in Poland without the notoriously harsh entrance examination. A year later, he became a finalist of the Physics Olympiad, which gave him the right to enroll, again without an examination, in any Physics/Mathematics department at any University in Poland. The physics department in the University of Warsaw, then called the Math and Physics Department, was the best place to study/work in Poland. One could say it was the crème de la crème of all academic units in Poland (Fig. 2).

The students and junior scientists with whom Alex was hanging out at that time were involved in adventure sports, such as climbing the Tatra Mountains, skiing, or sailing on the Masurian lakes. Alex was a pretty good rock climber and was admitted to the Polish Mountaineering Association (Fig. 2), a very elite organization. Alex's fascination with mountains has been visible throughout his life. At his current stage, he decided to establish his abode in the Appalachian Mountains, close to the Gambrill Park in Frederick, MD.

Fig. 1. A visit to the White House in 1962, hosted by President John F. Kennedy. Alex is identified by the red arrow.

After four years at the University of Warsaw, he chose biophysics as his MSc specialty. This newly emerging field was pioneered and organized in Warsaw by Prof. David Shugar. Then, in 1968, Poland saw increasing student unrest, leading to a nation-wide upheaval and demands for more freedom. The Polish authoritarian state panicked, and the government responded by sending police forces to subdue the academic institutions. Simultaneously, the government started an antisemitic propaganda campaign—applying the old maxim *divide et impera,* which very soon drove many talented people out of Poland. Alex's father lost his job, and the entire family was forced to emigrate with one-way passports.

While waiting for a US student visa, he worked for one year in the laboratory of Rita Levi-Montalcini (the 1986 Nobel Laureate) in Istituto Superiore di Sanita in Rome. In the United States, he was accepted into the Ph.D. programs of two universities and chose UCLA mainly because of its proximity to the mountains. Having good luck on his side, Alex found himself in the laboratory of David Eisenberg, another enthusiast of outdoor sports, where he became David's first Ph.D. student. Interestingly, years later, at the age of 70, David Eisenberg made a bike trip from Los Angeles to Virginia, confirming that he and his former protégé share not only a passion for science.

After receiving his Ph.D. in 1974, Alex moved to SSRL at Stanford. Together with Keith Hodgson, Margaret Yevitz Bernheim, James Phillips, and Julia Goodfellow (now Dame Julia Goodfellow), they constructed the first synchrotron station dedicated to single-crystal X-ray diffraction for macromolecular crystals [1]. Their demonstration of the feasibility of macromolecular synchrotron crystallography was a truly groundbreaking moment in structural biology, leading to a revolution in the way biostructural studies have been and are done. The Stanford group published a PNAS paper before two other seminal publications, from DESY (Hamburg) [2] and Novosibirsk (USSR) [3].

In 1976, Alex moved to the National Bureau of Standards (NBS, now NIST) to develop a macromolecular neutron diffraction station that utilized a new flat-cone neutron detector. In his free time, he worked on the structure of the Nerve Growth Factor (NGF), the protein hormone that was the focus of his fascination since his work in Rita Levi-Montalcini's

Fig. 2. Alex's Membership ID of the Polish Mountaineering Club.

laboratory. The most outstanding achievement at that time was the adaptation of the Konnert and Hendrickson's program PROLSQ for simultaneous X-ray and neutron structure refinement [4]. During that period, Alex established a very fruitful collaboration with the future Nobel Laureates Hans Deisenhofer and Robert Huber on the structure of bovine pancreatic trypsin inhibitor (BPTI) and with Tom Blundell (now Sir Tom Blundell) on the structure of NGF. The work on BPTI led to the first atomic-resolution structure resulting from joint neutron and X-ray refinement, which to this day is the gold standard for precision and accuracy in protein crystallography, especially for accurate modeling of hydrogen atoms [4]. Unfortunately, both the neutron and X-ray diffraction data from this pioneering experiment were permanently lost, which is one reason why Alex strongly advocates deposition of original structural data in dedicated repositories.

Around 1985, when interest for a wider application of neutron diffraction in macromolecular studies was waning, Alex got permission of the NBS authorities to establish a new laboratory dedicated primarily to X-ray crystallography. Alex's laboratory at the NBS significantly expanded when he hired Maria Miller, Gary Gilliland, Irene Weber, Rob Harrison, and others.

Around 1987, the National Cancer Institute (NCI) in Frederick announced plans to establish a structural biology laboratory and Alex Wlodawer was appointed to carry out this task. His group moved from NBS in Gaithersburg to Frederick (both in Maryland), with more hiring of international coworkers and collaborators (including one of the present authors). At the NCI, Alex Wlodawer assumed the laboratory chief position, and Irene Weber became a group leader. The NCI campus at Ft Detrick in Frederick became the haven where Alex has been working ever since. He established the first Macromolecular Crystallography Laboratory and held various directorial/chief positions in structural biology there. This period has been extremely productive, especially for medicinally important protein targets. In 1989, he published the first correct structure of a retroviral protease, derived from Rous sarcoma virus [5], which immediately became—even before publication—public property and the target of drug design efforts toward combating the devastating effects of AIDS due to the structural relationship between the RSV and HIV proteases [6]. This openness and free sharing in science is perhaps the most distinctive feature of Alex's philosophy of life. Experience has shown time and again that in the long run, this attitude will benefit everyone. In this case, a competing model of the HIV-1 protease was proved flawed, again based on a meticulously accurate experimental study by Alex Wlodawer [7]. The first structure of an inhibitor complex of HIV protease was also published by Alex's group [8]. In the following years, Alex solved the crystal structures of scores of proteases from a dozen or so of different retroviruses [9]. He is unquestionably the leading expert in the structural biology of retropepsins in the world. Alex's contribution to the structural biology of retroviruses also encompasses the viral integrase. He published the first crystal structure of the catalytic domain of wild-type integrase in its active conformation and complexed

with catalytic metal cations [10,11]. Among Alex's numerous other contributions to structural biology of human diseases and therapies is the discovery of the structure of bacterial L-asparaginase [12], which is a highly successful drug used to treat acute lymphoblastic leukemia (ALL). L-Asparaginase has been one of the leitmotifs throughout his entire scientific career, culminating in a recent opus magnum presenting the elucidation of the mechanism of these intriguing drug enzymes [13].

Apart from his considerable scientific achievements, Alex Wlodawer is a champion of quality and rigor in structural biological sciences. He is very well known for his efforts to maintain the highest standards of structural models and his desire to preserve their accuracy, precision, and reproducibility. He was the first to propose in 1997 the then revolutionary ideas that the structural models [14], and later (in 2007), that primary X-ray diffraction data [15] should be deposited and made available to the community. Subsequently, these initiatives were accepted as a rule by the International Union of Crystallography (IUCr), the Protein Data Bank (PDB) and almost universally by all reputable scientific journals, enormously increasing the level of reproducibility of crystallographic (and later also NMR and Cryo-EM) research. Access to structure factors and recently to raw diffraction data is one of the main reasons why structural biology is the most reproducible (and solid) branch of biological and medicinal sciences.

Structural biology has boomed in the previous two or three decades, and the techniques and methods have advanced to such an extent that even less experienced researchers now routinely use these experimental techniques. In light of these changing attitudes, many publications authored on Alex's initiative were presented with the intention to educate young structural biologists about the intricacies of the trade and ways to achieve results of the best quality [16-24]. Several collaborative papers were also dedicated to proper validation of atomic models of macromolecules and the identification of 'bad apples' among published results [25-30]. Recently, Alex has been instrumental in validating the structures of proteins from the SARS-CoV-2 coronavirus that are rapidly accumulating in the PDB in response to the COVID-19 pandemic [31-34].

As a long-time member of the Editorial Board of *The FEBS Journal*, Alex has also made immense contributions to the structural biology output at the journal, helping to uphold and progress standards in his this area, as well as serving as one of our most active editorial board members. Alex has also held the position of Features Editor at the journal for the past six years, developing and commissioning the Structural Snapshots series at the journal. As a handling editor, Alex's comments to authors are always insightful and helpful, while maintaining a critical perspective on the level of advance afforded by new manuscripts; not much escapes his keen eye! On more than one occasion, Alex has provided invaluable assistance to authors by spotting serious anomalies in their interpretation of structures that have greatly improved manuscripts prior to publication. He has been a champion for structural biology at the journal and has edited a number of Special Issues on Crystallography, including a Virtual Issue in recent months [35]. Alex's wry and ready humor enlivens editorial board meetings, and his unending passion for science and boundless curiosity concerning the natural world are truly inspirational.

It is clear that Alex is not 75 years old but 75 years young. He still hikes like a mountain goat, but he works now in a more relaxed way. Ten years ago, he was in the laboratory at 7:00 am sharp, including Saturdays. Today, he is a little lazy, and on Saturdays appears in the laboratory only at 8:15 am. He is still a champion for the quality of structures, inspirer of his collaborators, and tutor/helper for his people. Contrary to Frankenstein mentioned earlier, Alex is a real modern-time Prometheus who carries the torch of structure quality for better science and, in a pathetic dimension—for a better future. We do not expect that Alex will retire anytime soon. He published a dozen essential papers in 2019 and fifteen in 2020. His career and achievements are a true inspiration to young scientists, not only structural biologists.

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