Journal of Structural Biology 177 (2012) 3–13

Contents lists available at SciVerse ScienceDirect

Journal of Structural Biology

journal homepage: www.elsevier.com/locate/yjsbi

Looking back at a quarter-century of research at the Maurice E. Müller Institute for Structural Biology

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ARTICLE INFO

Article history:
Available online 17 November 2011

Keywords:
Actin
Aquaporins
Atomic force microscope
Intermediate filament
Nuclear pore complex
Scanning transmission electron microscope
Scanning tunneling microscope

ABSTRACT

The Maurice E. Müller Institute, embedded in the infrastructure of the Biozentrum, University of Basel, was founded in 1985 and financed by the Maurice E. Müller Foundation of Switzerland. For 26 years its two founders, Ueli Aebi and Andreas Engel, pursued the vision of integrated structural biology. This paper reviews selected publications issuing from the Maurice E. Müller Institute for Structural Biology and marks the end of this era.

1. Introduction

In November 1985 the Basel Department of Education and the Maurice E. Müller Foundation of Switzerland signed the contract for the operation of the "Maurice E. Müller Institute for High-Resolution Electron Microscopy" (MIH) within the framework of the Biozentrum of the University of Basel. The Maurice E. Müller Foundation has most generously supported this Institute over the 26 years of its existence, providing a total of approximately 40 million Swiss francs. Although its name later changed to "Maurice E. Müller Institute for Structural Biology", the abbreviation MIH survived and is used in this review. Charismatic Professor Maurice E. Müller[2] had a vivid interest in the development of the Institute and the people involved in building it up; he not only came to see the laboratories every year but also participated in the yearly MIH retreats, discussing with all MIH members and leaving a strong and encouraging impression.

The initial plan for the MIH proposed a unit for biomolecular microscopy that assesses the three-dimensional (3D) structure of biomolecules and their assemblies at close to atomic resolution. At that time fixed beam and scanning beam transmission electron microscopes were the tools of choice to achieve the visionary goals boldly formulated. While the selection of key biological projects was of most importance, progress in instrumentation and the development of sample preparation methods were part of the plan, as reflected by the statement in the proposal that '…the demand for more faithful imaging of biomolecules – ideally preserved in their native state requires developing novel sample preparation methods, more sensitive instruments, and more efficient image recording and processing. Continuous efforts in this interdisciplinary field between physics and biology are mandatory to elucidate the relationship between structure and function of biomolecules or specific assemblies thereof.'

In pursuit of its goals the MIH developed the vision of integrated structural biology research and produced about 660 articles, book chapters and international meeting contributions that have collected over the years over 28,000 citations (Fig. 1). The Institute also was strongly involved in training; in total 46 PhD students completed their degree pursuing projects at the MIH. MIH members have provided much of the biology teaching in the unique and interdisciplinary study program 'Nanoscale Sciences' of the University of Basel and contributed to the

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; AFM, atomic force microscope/microscopy; AQP, aquaporin; EM, electron microscope/microscopy; IF, intermediate filament; MIH, Maurice E. Müller Institute for High-Resolution Electron Microscopy/Maurice E. Müller Institute for Structural Biology; NE, nuclear envelope; NPC, nuclear pore complex; STEM, scanning transmission electron microscope/microscopy; STM, scanning tunneling microscope; TEM, transmission electron microscope/microscopy.

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[2] Maurice E. Müller (March 28, 1918 – May 10, 2009) was an outstanding orthopedic surgeon helping countless suffering human beings in Ethiopia, Europe and Switzerland. He founded Protek Ltd. to market the implants and tools he had invented and developed together with colleagues primarily for hip replacement surgery. The earnings flowed to the Maurice E. Müller Foundation for Continuing Education, Research And Documentation in Orthopedic Surgery, which since 1974 supports a large variety of research endeavors in the life sciences.

1047-8477/$ - see front matter
doi:10.1016/j.jsb.2011.11.013

Structural Biology and Biophysics as well as the Cell Biology program of the Biozentrum.

Major topics of the research conducted at the MIH include the study of filamentous structures, the nuclear envelope (NE) and membrane proteins in general, using a wide variety of conventional and unconventional biophysical methods. This review illuminates a few pertinent examples from a quarter-century of fruitful research.

2. The nuclear pore complex

An early contribution resulting from previous work demonstrated how the NE, the double membrane surrounding the eukaryotic cell nucleus, and its pore complexes are structurally organized by the intermediate-type filamentous meshwork of the nuclear lamina (Aebi et al., 1986a). Being the gateway to the nucleus, the nuclear pore complex (NPC) is among the largest molecular machines of the cell and composed of about 30 different proteins. The MIH reported the first solid data on the mass of native and membrane embedded nuclear pore complexes (NPCs; Reichelt et al., 1990). The measurement was made by scanning transmission electron microscopy (STEM), a technique developed at the Biozentrum Basel in the l970's and in use to the present day (Engel, 1978; Engel et al., 1976). The 8-fold symmetry of the 120 MDa NPC was clearly revealed by these experiments and mass maps of the native and detergent treated membrane embedded complexes were generated showing the contributions of their various rings (Fig. 2A). This paper heralded over 40 subsequent research papers addressing the complex and nuclear import/export. Work by the Aebi group helped to establish that NPCs are formed from a basic framework made of eight spokes embracing a central pore, a central plug or channel complex, a cytoplasmic ring from which eight short, highly twisted filaments emanate, and a nuclear ring with a basket-like assembly made from eight long thin filaments joined at their ends to form a distal ring (Jarnik and Aebi, 1991; Stoffler et al., 2003). This huge complex and its associated proteins mediate the active transport of proteins and RNAs as ribonuclear proteins. Particularly structural proteins, nucleoporins, were identified and investigated for roles in this active transport (Byrd et al., 1994; Guan et al., 1995; Siniossoglou et al., 2000; Yokoyama et al., 1995). The transport process was visualized in 1996 by monitoring the import of colloidal gold-labeled nucleoplasmin into the nucleus of Xenopus oocytes by electron microscopy (EM; Pante and Aebi, 1996; Fig. 2B). Nucleoplasmin bound first to the distal part of the cytoplasmic NPC filaments, which bent to transfer it to the cytoplasmic entrance of the central, gated, NPC channel. Like in this experiment, immuno-EM played a key role throughout the studies made, helping to localize some of the ~30 known nucleoporins (Fahrenkrog et al., 1998, 2002; Pante et al., 1997) including an NPC protein that interacts with the nuclear intermediate filament lamin A, a constituent of the nuclear lamina (Lussi et al., 2011). Developments in the scanning probe microscopies added another dimension to the research possible. Atomic force microscopy (AFM) was used to examine NPCs in a physiological environment (Goldie et al., 1994). Later AFM revealed more details (Fig. 2C) and calcium induced structural changes (Pante and Aebi, 1996; Stoffler et al., 1999). Recently progress made in sample preparation promises to allow nuclear transport to be directly visualized (Huang et al., 2010); the binding of gold-tagged antibodies has already been detected. Furthermore, force interactions measured by atomic force microscopy (AFM) have revealed how the natively unfolded, phenylalanine–glycine rich

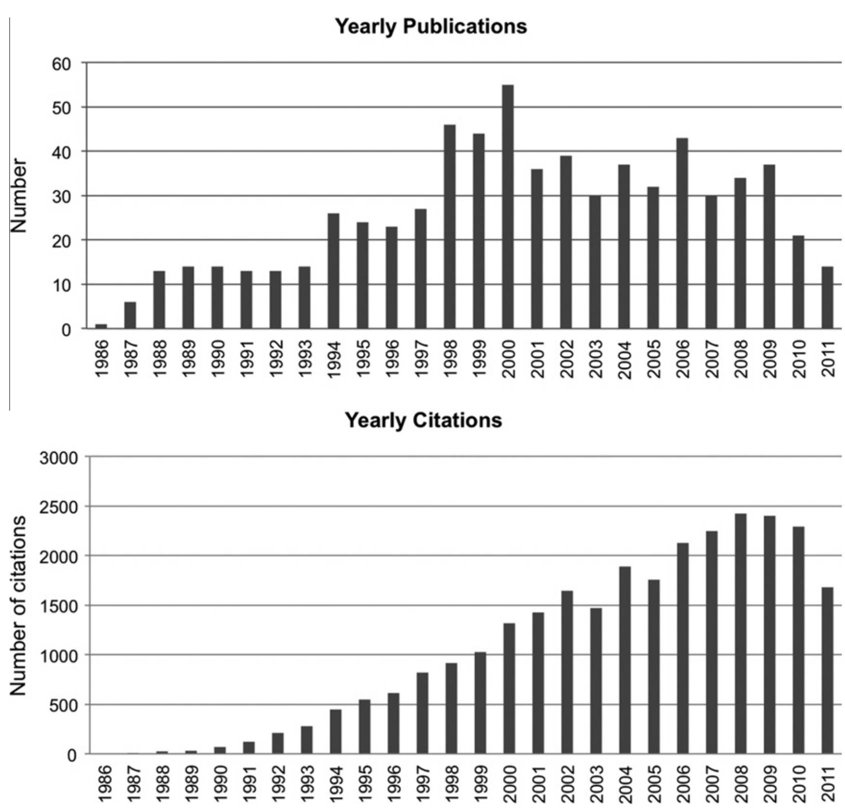

Fig.1. MIH publications and citations. The average productivity was 25.5 publications/year over 26 years or 663 publications overall. The quality of this work is measured by how many times these publications were referred to (lower graph). In total MIH papers have been cited 28,915 times, 43.5 time/publication on average, yielding an h-index of 94. The top scoring publications (>200 citations) were published between 1986 and 2006, documenting that the high was standard of the Institute maintained throughout its existence. Taking into account the financial support by the Maurice E. Müller Foundation, the Swiss National Foundation for Research, and the European Commission, one MIH publication came to a cost of ~100,000 CHF, not including the infrastructure provided by the University of Basel. (Analysis accomplished using apps.webofknowledge.com.)