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2016 Lasker~Koshland to Bruce Alberts

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The 2016 Lasker~Koshland Special Achievement Award will be presented to Bruce Alberts for a lifetime career of outstanding scientific discovery and inspiring leadership and mentorship in promoting fundamental research, science education, and rational, evidence-based values worldwide.

A picture can be worth a thousand words—and sometimes many more. At the National Academy of Sciences, Bruce Alberts's portrait was unveiled in 2005 at the completion of his two-term NAS presidency (Figure 1). Unlike those of the 19 distinguished men who preceded Bruce at the helm of that staid organization—launched by Abraham Lincoln to advise government on matters of science—the painting captures Bruce wearing a broad smile and a tie that beams over a dozen emojis hell bent on out-smiling him. Thinking that the portrait implies that Bruce took a casual approach to the Academy's mission would disregard the entirety of his 12-year legacy.

Indeed, Bruce's distinctive activities at the NAS emerged as deeply impactful elements in national science policies and education, punctuating his remarkable career-spanning contributions, which collectively will be honored by the 2016 Lasker~Koshland Special Achievement Award in Medical Science, one of the highest recognitions of science in the US. Bruce will receive the award "for fundamental discoveries in DNA replication and protein biochemistry; for visionary leadership in directing national and international scientific organizations to better people's lives; and for passionate dedication to improving education in science and mathematics." Taking similar notice, President Obama foreshadowed this year's Lasker jury decision, presenting Bruce with the National Medal of Science in 2014.

Bruce currently holds the position of Chancellor's Leadership Chair for Science and Education in the Department of Biochemistry and Biophysics at the University of California, San Francisco. As a Harvard freshman, he was inspired by the late John Moore's 1957 textbook, *Principles of Zoology* (Moore, 1957), which framed biological concepts as broad ideas to be embraced or challenged, a dramatic break from the then-current way of science teaching comprised entirely of memorizing lists of facts, such as the details of metabolic pathways and the nomenclature of organisms or body parts. Moore and his book "brought science to life as an exciting and profound human endeavor" (https://brucealberts.ucsf.edu/wp-content/uploads/2016/05/moore-john-a.pdf). Enamored with Moore's approach, Bruce fashioned for his PhD research a seductively creative yet overly narrow model for the mechanism of initiation of DNA replication. Failure to confirm his model turned into a "wake up call" when his thesis committee declined to award his degree, delaying the imminent start of his postdoc at the University of Geneva (Alberts, 2004)

Bruce absorbed from his failure a broad lesson: biology is complex. Thus, any specific model, no matter how pleasing on first principles, is unlikely to be correct. In response, he refined his research strategy during his postdoc years, consciously developing approaches that would advance knowledge independent of any particular preconceived model. Still focusing on the mechanism of DNA replication, he developed this time a general strategy instead of pursuing a circumscribed idea. He fashioned DNA-cellulose, the first affinity chromatographic matrix using a biological molecule as capture agent, to identify DNA-binding proteins that might be involved in replication. As an assistant professor at Princeton, he combined his catalog of biochemically identified DNA binding proteins with the extensive set of bacteriophage T4 replication defective mutants collected by Richard Epstein in Geneva and colleagues at Caltech. He exploited the capacity to produce preparative amounts of those proteins from T4-infected *E. coli* to develop an in vitro complementation strategy that validated their significance to the replication process, facilitated their purification, and at the same time illuminated their functions.

Armed with his hard-won insights into research strategic planning, Bruce launched his independent career at Princeton. One of us (K.R.Y.) was fortunate to be assigned for a summer research rotation prior to the beginning of first-year classes and was later privileged to become the second graduate student in his lab. Bruce's rigorous yet remarkably generous mentoring and his efforts to enliven science education were already in bloom: when the pre-first year rotation student refined a method that Bruce had been developing for harvesting phage, Bruce arranged for the rotation student—rather than for himself—to present a talk at the prestigious Cold Spring Harbor Phage Meeting; when that same graduate student declared interest in eukaryotic transcriptional regulation rather than T4 replication, Bruce not only assented but deeply engaged in the project rather than demanding coherence of investigations in his small lab. He also

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helped arrange for a leave for that graduate student, by then in his fourth year, to work full time in George McGovern's presidential campaign—and then to return to complete graduate school, helping him to publish one of his papers as sole author. Bruce created an energetic research environment, held to high standards and expectations, simultaneously challenging and joyful. And, instead of spending every waking hour pressing his own research, Bruce started a program that brought high school students to Princeton for fun days of hands-on science, cementing a foundation of concept-driven learning and a developing a growing appreciation for how effective science education could at the same time nurture intellectual power and foster social impact.

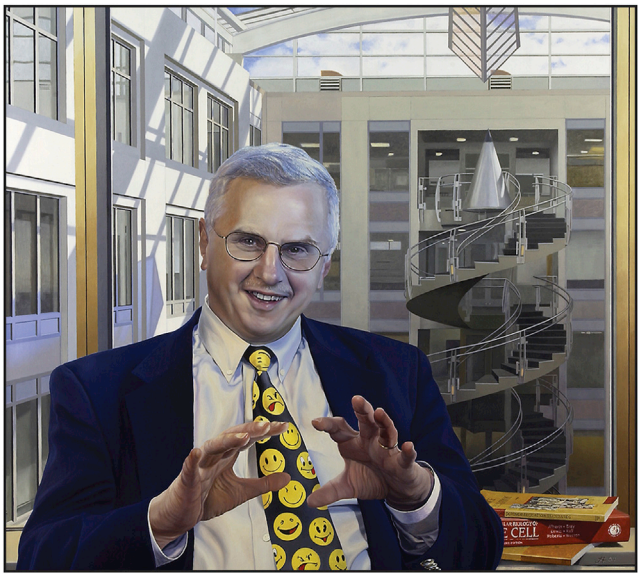

Figure 1. A portrait of Bruce M. Alberts as the Twentieth President of the National Academy of Sciences

The portrait hangs in the National Academy's Keck Center. Credit: Jon Friedman, *Bruce Alberts*, 2004, oil on linen.

Throughout his time at Princeton—and after his move in 1976 to UCSF—Bruce made seminal methodological and experimental contributions and unveiled brilliant intellectual insights that advanced our understanding and thinking about DNA replication—its initiation, its processivity, and its fidelity. Following his isolation of T4 gp32, his demonstration that it bound selectively and cooperatively to single-stranded DNA, and his deduction and subsequent proof that it unwinds double helical DNA ahead of the advancing DNA polymerase, Bruce employed his in vitro complementation assays to isolate and initially characterize six additional factors. In a tour de force, his laboratory reconstituted the replication process using these purified proteins, demonstrating necessity and sufficiency.

Most importantly, Bruce discovered that the replication proteins assemble into a large functional complex. This realization, founded on solid experimental results rather than imaginative speculation, suggested a way that polymerases, various other enzymes and structural components that each previously had been shown to operate separately on the leading and lagging DNA strands, might themselves interact to form an integrated assembly, a supra-molecular "protein machine" that drives replication. Amplifying on this concept, Bruce demonstrated that such multicomponent protein machines can themselves form yet higher-order assemblies as underscored by the coupling of T4 DNA replication and recombination/repair. These insights led him to suggest that cells are collections of macromolecular machines (Alberts, 1998), organized, functioning, and interacting, within the constraints of evolution, according to engineering principles. By suggesting that such machines carry out every major cellular process, that specialty factors attach transiently to provoke specialized activities such as initiation or elongation, and that inter-machine interactions produce inter-process interactions potentially with emergent properties, Bruce's work changed thinking, education, and experimentation across cell and molecular biology. The concept that protein machines, that is, assemblages of stable and dynamic components functioning cooperatively, execute complex cellular transactions is now a generally accepted paradigm that drives experimental design and interpretation.

With his fertile scientific intellect and stellar research contributions, his deep commitment to essential science education, and a remarkable clarity of vision for policies and practices that would advance or improve both research and education, Bruce juggled a daunting blend of research, education, and administrative responsibilities for over two decades. The balancing act began just 7 years after his appointment to the Princeton faculty, when he became Acting Chair of Biochemical Sciences. Indeed, he moved to UCSF as Vice-Chair of the Department of Biochemistry and Biophysics, where he contributed to seeding what would become one of the most renowned biological research communities worldwide. In 1985, he assumed the chairmanship of the department, just as he was developing new experimental approaches to a new research focus, centered on the role of the cytoskeleton during early development. As with bacteriophage T4, Bruce chose an experimental system, *Drosophila melanogaster*, which was richly grounded in genetics and, in addition, enjoyed elegant classical cytological and cell biological description. Bruce developed and was refining novel approaches to access and analyze actin binding proteins and the centrosome to probe the functional organization and interplay of cytoplasm and nuclei during the highly stereotyped dynamics of some of the earliest developmental stages.

That exciting new effort was cut short, however, when Bruce accepted election in 1993 to the presidency of the National Academy of Sciences (NAS), reluctantly closing his lab soon after moving to Washington DC. As NAS president and chair of the National Research Council (NRC), his vision was global and an echo of his character:

> To dream about a nation, and a world, that is permeated by the best representations of science and scientific values—honesty, generosity, a respect for evidence,

and openness to all ideas and opinions irrespective of their source (Alberts, 1999).

He excited and inspired by enunciating key issues, including many viewed as challenging or impossible, and by investing enormous energy and leadership in seeing them to fruition. He developed the first National Science Education Standards and then helped build tools to enable teachers and school boards to meet them. As NRC chair, he brought young scientists into the science policy arena by launching the prestigious Christine Mirzayan Science and Technology Graduate Fellowship Program, and he oversaw publication of nearly 200 National Research Council reports focused on education. As NAS president, he advanced public understanding of the societal contributions of basic science through a 20-part series, "Beyond Discovery: The Path from Research to Human Benefit," (http://www.nasonline.org/publications/beyond-discovery) and by opening the Marian Koshland Science Museum at the NAS in Washington. In short, he impacted the world as the "Education President" of the NAS.

As a global ambassador of science and science education, Bruce traveled the world, building lasting, trusted relationships with governments and science academies in Asia, Africa, the Middle East, South America, and elsewhere. He helped to launch two formal networks, the InterAcademy Panel, which brings together science academies and assists formation of new ones, and the InterAcademy Council, which Bruce co-chaired for its first decade, mobilizing global scientists and engineers to advise the United Nations, the World Bank, and other international groups. Later, he answered the call from President Obama to serve for 2 years as a Science Envoy for the U.S. Department of State to Indonesia and Pakistan, helping to connect and empower the next generation of scientific leaders to work across national and religious boundaries and across a wide spectrum of disciplines. This last appointment overlapped by a year with a nearly 5 year tenure as Editor-in-Chief of *Science*, a bully pulpit from which Bruce promoted changes in NIH policy, and improved science education at all levels. He emerged as a passionate advocate for curiosity-driven investigator-initiated research and sounded an alarm against expanding support for translational research with narrow clinical goals at the expense of open-ended approaches that have consistently produced broadly impactful, path-breaking, and paradigm-changing discoveries. These timely arguments, so important to the science community at large, seemed to mirror and amplify Bruce's personal lesson, learned many years before, about the relative value of research that could expand general knowledge as opposed to potentially validating a particular idea. Much earlier, Bruce had astutely equated the value of artesian bread made in small family-run bakeries versus the output of Wonderbread factories in order to promote small, creative labs over huge groups pushing massive efforts of sometimes questionable value toward pre-envisioned endpoints (Alberts, 1985).

Bruce's engagement as proponent of fundamental scientific research remains strong, as evidenced by his current leadership in addressing the research and training funding crisis in the US. Along with Marc Kirschner, Shirley Tilghman, and Harold Varmus, Bruce suggested that a national morale crisis in biomedical research has been driven by perceived flaws in the system of funding and managing the scientific enterprise. The "Rescuing Biomedical Research" (http://rescuingbiomedicalresearch.org/) effort seeks to identify and address important and frustrating barriers to effective science and to re-think elements of the infrastructure that supports biomedical research in this country. Bruce's leadership and unwavering concern for young scientists has been a key driver throughout.

Throughout his career, Bruce has promoted the philosophy that science and science education enable societal progress—that citizens who demand evidence-based decision-making create stronger, more just societies that could counterbalance irrationalities that govern much of current world affairs. Beginning with the notion that all children are born as innate scientists, eager to understand the world around them, underscored by the inevitable "Why"? phase that parents of every preschooler know so well, Bruce has sought to build and amplify that innate curiosity and to counter education systems that feed facts and test for prepackaged answers. His NAS portrait reminds us all: science is fun! In 1987, Bruce founded the Science and Health Education Partnership (SEP) that brings together scientists from UCSF and teachers of the San Francisco Unified School District as partners promoting curiosity, seeking evidence and celebrating discovery. As lead author of one of most renowned cell biology textbooks—"Molecular Biology of the Cell"—Bruce used his personal share of the book's royalties to launch SEP. Some 30 years later, SEP is firmly established as an institutionally supported, national and international model of science education, bringing together hundreds of practicing scientist volunteers — graduate students, postdocs, technical staff, and faculty — in a true partnership with K–12 teachers in virtually every San Francisco public school. In 2011, SEP was honored by the White House with the Presidential Award for Excellence for Science, Mathematics, and Engineering Mentoring. True to John Moore's principles, SEP supports inquiry—not regurgitated facts—as a way of learning and knowing.

The same concept applies to the textbook. Challenged by Jim Watson in 1978 to write a textbook that would cover the then-evolving confluence of molecular and cell biology, Bruce and a team of pioneering authors struggled for 5 years until a first edition was crafted that succeeded in defining the field by its fundamental principles rather than disembodied lists of factoids. *Molecular Biology of the Cell*, now in its sixth edition, has helped generations of budding young scientists to find a firm footing based on established concepts and acknowledgment of the vast open spaces for new discovery. As co-author on recent editions, one of us (PW) enjoys the privilege of working with Bruce on this effort, whose success reflects his leadership style, which fosters the author team, inclusive of publishers, editors, illustrators, spouses, and children, to function as an expansive family with a common purpose.

Just as the expansive legacy of his NAS presidency might contrast to his whimsical portrait, Bruce appears to present

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many contradictions. He is, indeed, at the same time strong and humble, tough and warm, discriminating and inclusive, awe inspiring and approachable, visionary and razor focused. Yet these seemingly contradictory characteristics simply reveal different facets of his character—unassuming brilliance, optimistic humanism, quiet self-confidence, absence of ego—that have made his work so important and him so impactful across the arc of our science endeavor. For over four decades, as an individual scientist, an academic scholar and educator, a national and international leader, Bruce Alberts has profoundly and distinctively advanced science and science education and has engendered a deepened scientific perspective on public discourse and public policy.

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