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Interview with Aaron Ciechanover

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Biochemical and Biophysical Research Communications (BBRC) thought it would be interesting to ask Aaron Ciechanover a few general questions on scientific editorial policy, on the way science is viewed and evaluated today, and (more generally) on the changes in the area of biochemistry and biophysics since BBRC was initiated. Below are our questions and his answers. The interview was conducted by Dr. Ernesto Carafoli.

BBRC: You indicated several times, during your lectures and in your writings, that you have a warm spot in your heart for *Biochemical and Biophysical Research Communications.* Why?

Ciechanover: Indeed, this is true. As a graduate student with Avram Hershko, we published our first study on the ubiquitin system in BBRC. At that time, we never dreamed that it was going to become the ubiquitin system as we currently know it, but in retrospect it was clearly the first paper in the field, and like a first love, one always remembers it. Yet it was not only the first study but also a very important one, because it paved the road to the discovery of the multicomponent ubiquitin system. Already at that early stage, it was clear that the proteolytic activity in the crude reticulocyte lysate is not catalyzed by a single "classical" protease, as had been the paradigm in the field of proteolysis, but rather by a two-component system—and probably a more complex one. Furthermore, we showed in this study that one of the components is a small, approximately 8 kDa heat-stable protein, which predicted some unusual characteristics of the system. Further studies that followed this pioneering BBRC paper showed that the basic assumptions and predictions made in this paper were true, and that the methodological lesson was well learned; whenever we lost activity during the purification steps, we searched for it—via a complementation assay we set—in the chromatographically resolved fractions. This enabled us to discover the basic components of the system and to reconstitute, step by step, the two-stage mechanism of proteolysis—tagging of the substrate with ubiquitin that is followed by its degradation.

BBRC: What do you think has been the role of BBRC in shaping the life sciences landscape during the past 50 years? Along with it, could you give us your appraisal of the merits and demerits of "niche" journals as opposed to all-encompassing journals?

Ciechanover: BBRC played a major role from the 1950s to the 1980s in bringing to the reader the general and major developments in biochemistry and biophysics. With almighty editors like Bernard Horecker and William McElroy, it brought the best in those fields. Yet winds changed direction in the scientific community, specialization increased, methodologies and platforms changed, and the focus of many turned to the study of disease mechanisms and then to "translational" research. Niche journals appeared, and the "molecular biological" revolution has cornered classical biochemistry. The exponential growth in the number of researchers in life sciences between the 1970s and the 1990s, along with the tough competition for research funds and the development of new computational tools to follow research output, has crowned new gods—the bibliometric values—and BBRC, loyal to the "old" values, has remained behind, I fear. Yet we should not forget that proteins are the organism's core elements, and we are still far from understanding their structure and the mode of action of most of them. The pendulum has started its move back, and rather quickly we are entering the postgenomic era—the era of the proteins. Researchers will use more sophisticated tools than in the past when studying proteins, but the glorious days of biochemistry will be back, though dressed differently. As for niche journals versus all-encompassing journals, I somewhat prefer the latter because they give a broader view of new trends and the whereabouts in areas that are not represented in the more specialized journals.

BBRC: In the past, glorious periodicals like the *Journal of Biological Chemistry* (JBC) were the dream of any researcher. Now these journals are shunned by young researchers who prefer trendy, high-impact factor niche journals. Can you comment on this?

Ciechanover: This is true and saddening. It reflects a broader phenomenon where the entire academic system—universities that promote researchers and agencies that fund their research—has been enslaved by the new religion of bibliometrics. The decision makers, to a large extent, evaluate researchers by a set of numbers and, as a result, do not assess seriously the ideas that are behind the research, the depth and potential of the research, and the ability of the scientist to carry out his or her ideas. Numbers are easy to evaluate and compare, and the scientific community escaped from its duty in many ways and chose the easy "solution." No wonder researchers are also affected in their choice of a publication platform; they realize that BBRC and the like can no longer carry them to promotion, tenure, funding, and fame. It is sad, especially nowadays when we do not read journals but rather look for articles of interest in databases, where we can find what we are after regardless of the journal in which it was published. As a result, the numerical values have remained tools not for promoting sciences but rather for promoting people. It should be admitted that bibliometric evaluation has a value, but in a much broader context. It is one single parameter that can be biased and, therefore, should be used cautiously. The problem is that the ease of use of these data

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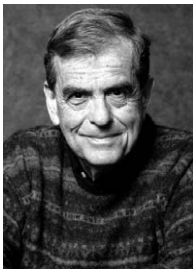
amplified their role much beyond their real value and led to abandonment of other, more valuable, yet admittedly harder to use tools—evaluating the scientist and his or her research. Beyond the bibliometric issue, there is another problem in that many of the high-impact factor niche journals belong to private publishers, while many of the less glorious all-encompassing ones are published by professional societies. This brings up the issue of free access to the knowledge generated in research institutions, because we should not forget that most of the research is funded by public money—by the taxpayers; therefore, in many ways, its results belong to the public, at least the right to have free access to the findings. Journals that belong to professional/public organizations, like JBC and *Proceedings of the National Academy of Sciences of the USA* (PNAS) and the journals of the American Society for Microbiology (ASM) and the Federation of the European Biochemical Societies (FEBS), are more keen and liberal in their approach on allowing free access than the privately owned journals. There is something morally wrong when the public has to pay for-profit companies in order to have access to data that were generated with its own support. I think that in that respect, the *Public Library of Science* (PLoS) journals are a good example for how to solve this problem. These are highly respected, professionally peer-reviewed journals that ask the authors to pay a one-time maintenance fee to keep the articles on the central computer server, and the articles become freely accessible by the entire public from the day they are published.

BBRC: BBRC was initiated as a vehicle to promote dissemination of novel knowledge in biochemistry and biophysics. Things have changed, and an approach that is more cell biological in nature has taken primacy. Is there a risk that the quantitative character that was the hallmark of biochemistry and biophysics will get lost?

Ciechanover: I do not see such a risk. We should not forget that biochemical analysis requires interference with the events that occur in the intact cell. We break cells open, isolate enzymes by different techniques that separate them from other components, and attempt to reconstitute processes, at times by adding nonphysiological amounts of reagents. This approach has had a tremendous value in deciphering a broad array of mechanisms and processes. Yet it is also destructive in many ways, and does not allow examination of processes in their cellular context, movement of proteins between organelles, monitoring of effects of modulating agents on cellular processes, and so on. More recent discoveries and developments, like the discovery of the fluorescent proteins, allow us to become observers, to follow processes from the side without intervening, allowing the processes to occur in the natural environment—in the cell, and even in the entire organism. Yet this type of analysis via indirect routes also has disadvantages, especially in attempts to reconstitute multicomponent pathways where steps are executed sequentially. Thus, although the ubiquitin system could possibly not have been discovered using a cell biological approach, the discovery of degradation of proteins from within the endoplasmic reticulum (endoplasmic reticulum-associated degradation) could not have been discovered without using a combination of cell biological and genetic tools. I believe that using a blend of "pure" quantitative approaches along with more "holistic" approaches will give us the correct view of events occurring in the cell and then in the whole organism. Each approach and each technological platform has its own merits, advantages as well as shortcomings, but they are complementary.



Aaron Ciechanover: Aaron Ciechanover was born in Haifa, Israel in 1947. He received his M.Sc. (1971) and M.D. (1975) from the Hebrew University in Jerusalem, and his D.Sc. (1982) from the Technion-Israel Institute of technology in Haifa, Israel. There, as a graduate student with Dr. Avram Hershko and in collaboration with Dr. Irwin A. Rose from the Fox Chase Cancer Center in Philadelphia, USA, they discovered that covalent attachment of ubiquitin to a target protein signals it for degradation. Using a reconstituted cell free system, they purified the basic conjugating enzymes, deciphered their mechanism of action, described the basic proteolytic function of the system in cells, and proposed a model according to which this modification serves as a recognition signal for a specific downstream protease. As a post doctoral fellow with Dr. Harvey Lodish at the M.I.T., and in collaboration with Drs. Dan Finley and Alexander Varshavsky, they described a cell with a mutation in the first enzyme of the ubiquitin system, which further corroborated earlier findings, but also predicted the involvement of ubiquitination in regulating several basic cellular processes such as quality control and cell cycle. Since 1984, he is on the academic staff of the Faculty of Medicine of the Technion. Along the years it has become clear that ubiquitin-mediated proteolysis plays major roles in numerous cellular processes, and aberrations in the system underlie the pathogenetic mechanisms of many diseases, among them certain malignancies and neurodegenerative disorders. Consequently, the system has become an important platform for drug development. For the discovery of the ubiquitin proteolytic system, Ciechanover, Hershko, and Rose were awarded the 2004 Nobel Prize in Chemistry.