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Enabling technologies in discovery: the 2009 Nobel Prize and its implications in antibiotic design

Yinan Wei and Sylvia Daunert

Department of Chemistry, University of Kentucky, Lexington, KY 40506-0055, USA

Every year in early October the announcement of the winners of the Nobel Prize in different disciplines, including those awarded the Nobel Prize in Chemistry, is greeted with expectation and often surprise by the scientific community. Despite its many detractors claiming unjust and even political choices of the awardees, the Nobel Prize still carries an aura of scientific glamour that no other prized award in science or medicine does. The *2009 Nobel Prize in Chemistry* recognized three researchers for elucidation of the structure and function of the ribosome, the protein production machinery that translates the DNA blueprint of life into life itself. The laureates, *Venkatraman Ramakrishnan* (MRC Laboratory of Molecular Biology, Cambridge, UK), *Thomas A. Steitz* (Yale University, CT, USA), and *Ada E. Yonath* (Weizmann Institute of Science, Rehovot, Israel) exemplify the spirit of scientific devotion that has long resulted in breakthrough discoveries. The road leading to the atomic resolution structure of the ribosome was a long journey. Ribosomes are large RNA-protein complexes. Obtaining the ribosomes at high purity and in large enough amounts to perform meaningful studies was, in itself, already a formidable task. The pinnacle of many years of tenacious work by Yonath and colleagues was the crystallization of the ribosomal 50S subunit from the thermophilic bacterium *Geobacillus stearothermophilus* [1]; this was the first true breakthrough leading to the elucidation of the structure of the ribosomes. In the next two years a few other ribosomal subunits were crystallized, but most of them did not render enough diffraction resolution (i.e., only 10 Å) to build a structure model with high fidelity. It took Yonath and colleagues ten full years to reach the second milestone in the revelation of ribosome structure when they finally obtained crystals from the 50S subunit from *H. marismortui* with a diffraction resolution of 3 Å [2]. Strikingly, while it took almost two decades to advance from the first crystal to the low resolution structure, it took merely three years to move the resolution of the 50S subunit structure from low [3], via intermediate [4–7], to high [8–11]. This fast progress is largely because of improvement of other analytical methods that aided in the task, such as the employment of CCD area-detectors for precise and automated analysis of X-ray diffraction patterns.

The ribosome is the bridge between the blueprint of life, the genetic information encoded in DNA, and the executors of life, the proteins. Thus, determining its structure and gaining insight into its detailed mechanism of function is of critical importance. Further, the relevance of these studies is also compounded by the fact that about half of the currently employed antibiotic compounds act on the ribosome [12,13]. The structures of the prokaryotic and eukaryotic ribosomes are quite different, although their basic working mechanisms are similar. Many antibiotics capitalize on these differences to selectively or preferentially target the prokaryotic ribosome to attack a vast array of microorganisms and disrupt their protein synthesis. In the past two decades, there has been an explosion in the determination of crystal structures of

ribosomes with bound drugs. These include the revelation of the 50S ribosome unit complexed with antibiotics of the macrolides, ketolides, streptogramins, lincosarnides, pleuromutilins, phenylpropanoids, oxazolidinones classes, and the 30S ribosome complexed with aminoglycosides, tetracyclines, edeine, pactamycin, spectinomycin, and with other families of antibiotic compounds. A better understanding and clearer view of the mechanism of protein synthesis inhibition by these drugs will facilitate and inspire the structure-based design of novel antibiotics, an issue of critical importance given the increasing prevalence of bacterial resistance to existing drugs.

The major milestone behind the ribosome work was the development and improvement of X-ray crystallography techniques, which belong within the broad realm of physical analytical science. With the boundaries between different branches of chemistry becoming less and less defined and more transparent, there are very few chemists who can solely define themselves as classical analytical chemists. The traditional definition of analytical chemistry is the “branch of chemistry that involves the quantitative and qualitative analysis of compounds with no specific regard to the identity of the compound”. Modern analytical science is focused on the design and development of enabling techniques and instrumentation for targeted applications. Many of today's analytical chemists work at the interface of disciplines with the goal to build new tools that will help achieve a better understanding of a specific subject or system. It is not unusual to find analytical chemists among the most prominent contributors to biological, biomedical, physical, clinical, materials, or environmental research and to different fields of engineering. Bearing this in mind, although this year's Nobel Prize was not awarded directly to researchers in the field of analytical chemistry, it certainly has highlighted the steady improvement of a physical method with an analytical component—X-ray crystallography, which has made the high resolution three-dimensional structure of the ribosome available to many researchers.

The three laureates are not the first crystallographers honored by the Nobel committee with the prize. Since W.C. Röntgen was first awarded the Nobel Prize in Physics for the “Discovery of X-rays” in 1901, awards that are directly related to, or that involved the use of crystallographic methods and techniques are numerous. In the early days the awardees' work was primarily associated with the development of the instrumentation and methodology—examples include M. Von Laue (1914 Physics, diffraction of X-rays by crystals), W.H. Bragg and W.L. Bragg (1915 Physics, use of X-rays to determine crystal structure), and J.B. Sumner (1946 Chemistry, discovery that enzymes can be crystallized). In more recent years, a variety of scientists have been awarded the Nobel Prize for their work using X-ray crystallography to solve physical, chemical, and biological problems, with three out of the nine prizes in chemistry since 2001 presented to crystallographers (this year's laureates along with R.D. Kornberg in 2006 and R. MacKinnon in 2003). While some of the award-winning scientists are not analytical chemists, the development and implementation of analytical instrumentation and techniques has invariably played an important role in their path to discovery.

Many scientists have been recognized by the Nobel Prize for their contributions to the development of what we could define as broad-spectrum analytical science. A list of milestone contributions to the improvement of analytical instrumentation and/or methods is shown in Table 1. The most recent award in analytical chemistry per se was the 2002 Nobel Prize in Chemistry, which went to J.B. Fenn and K. Tanaka, for the development of soft desorption ionization methods for mass spectrometry, and to K. Wüthrich, for his development of nuclear magnetic resonance spectroscopy for determining structures of biological macromolecules in solution. Other examples of enabling technologies that have affected measurement science can be found in areas covering both chemistry and physics (Table 1). For example, Willard Boyle and George E. Smith shared the 2009 Nobel Prize in Physics for the invention of the imaging semiconductor circuit, namely the CCD sensor. CCDs have revolutionized photography and

are used extensively as detectors in many analytical instruments. Indeed, the introduction of CCD area-detectors played a critical role in the determination of the high resolution structures of ribosomes described above [14].

In examining the traditional definition of analytical chemists, we should emphasize that it falls short of the role that these scientists play in the advancement of 21st century science and technology. Analytical chemists are not only measurement chemists, but also inventors and enablers of state-of-the-art technologies. With the interface between different fields of modern sciences constantly changing and evolving, researchers need to be adept to work at interfaces between disciplines, and thus the definition of analytical chemist evolves with the development of analytical science. The improvement of instrumentation and analytical techniques is usually driven by the desire to investigate a certain scientific problem and/or the lack of adequate tools to gain insight into an area of research. As stated above, perhaps a more proper definition of analytical chemists could be “measurement scientists, instrument designers, and enablers of technologies”. It is clear that analytical science has evolved into an integrated part of all fields of chemistry. Without analytical approaches experimental science is simply impossible. The importance of analytical chemistry is reflected by the many prizes awarded to recognize contributions from scientists who pioneered or drastically improved an analytical method or designed and developed new instrumentation.

We live in an era filled with expeditious progress in science and technology where breakthroughs in one area of science permeate to others and progress is achieved in an exponential manner. Scientists are as excited as children anticipating candy to learn about the next breakthrough in analytical instrumentation or method that will enable them, for example, to push the detection limit of their target analyte to single molecule levels in real time with tremendous specificity and in a complex sample matrix. Will the year 2010 and beyond bring breakthrough(s) that will help elucidate important structures and mechanisms of life such as crystallography did for the ribosomes? The answer is: SURE! Which ones? Time will tell, but along the way we hope that the enablers of science, namely analytical chemists, will be recognized in the future for their efforts and contributions. Analytical chemists are pushing the limits of measurement science, and enabling technologies are benefiting not only research, but also the daily lives of people at many levels, from providing a cleaner environment to improving medical diagnostics and healthcare. Thus, it seems only fair that the work of analytical chemists be deemed as important as that of the scientists who have been enabled to perform their research thanks to them. While there has been over the years some of that recognition, it is not nearly enough nor does it favorably compare with that received by the scientists who actually profit from analytical chemists’ ingenuity and perseverance in instrument design and method development. It is about time that analytical chemists get the credit they deserve!

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Biographies

Yinan Wei joined the faculty of the Department of Chemistry, University of Kentucky as an Assistant Professor in 2008. Her research interests include the study of proteins involved in the multidrug resistance, investigation of the membrane protein folding pathway, and development of biosensors for the detection of pathogenic microbes.

Sylvia Daunert is Gill Eminent Professor of Analytical and Biological Chemistry, Professor of Chemistry, and Professor of Pharmaceutical Sciences, Biological and Bioanalytical Chemistry at the University of Kentucky, Lexington. Dr Daunert's research group uses recombinant DNA technology to design new molecular diagnostic tools and biosensors based on genetically engineered proteins and cells for applications in biomedical and environmental fields. Additionally, her research focuses on the design of sensing arrays for the detection of molecules in small volumes and microfluidic platforms, and in the development of smart biomaterials for responsive drug-delivery systems. Among other awards and distinctions, she received a Fulbright Scholarship, and is the recipient of the 2001 A. F. Findeis Award from

the American Chemical Society, and the 2002 Special Creativity Award of the National Science Foundation.

References

1. Yonath A, Mussig J, Tesche B, Lorenz S, Erdmann VA, Wittmann HG. *Biochem Int* 1980;1:428–435.
2. von Bohlen K, Makowski I, Hansen HA, Bartels H, Berkovitch-Yellin Z, Zaytzev-Bashan A, Meyer S, Paulke C, Franceschi F, Yonath A. *J Mol Biol* 1991;222:11–15. [PubMed: 1942063]
3. Ban N, Freeborn B, Nissen P, Penczek P, Grassucci RA, Sweet R, Frank J, Moore PB, Steitz TA. *Cell* 1998;93:1105–1115. [PubMed: 9657144]
4. Ban N, Nissen P, Hansen J, Capel M, Moore PB, Steitz TA. *Nature* 1999;400:841–847. [PubMed: 10476961]
5. Clemons WM Jr, May JL, Wimberly BT, McCutcheon JP, Capel MS, Ramakrishnan V. *Nature* 1999;400:833–840. [PubMed: 10476960]
6. Tocilj A, Schlunzen F, Janell D, Gluhmann M, Hansen HA, Harms J, Bashan A, Bartels H, Agmon I, Franceschi F, Yonath A. *Proc Natl Acad Sci USA* 1999;96:14252–14257. [PubMed: 10588692]
7. Cate JH, Yusupov MM, Yusupova GZ, Earnest TN, Noller HF. *Science* 1999;285:2095–2104. [PubMed: 10497122]
8. Ban N, Nissen P, Hansen J, Moore PB, Steitz TA. *Science* 2000;289:905–920. [PubMed: 10937989]
9. Nissen P, Hansen J, Ban N, Moore PB, Steitz TA. *Science* 2000;289:920–930. [PubMed: 10937990]
10. Wimberly BT, Brodersen DE, Clemons WM Jr, Morgan-Warren RJ, Carter AP, Vonnrhein C, Hartsch T, Ramakrishnan V. *Nature* 2000;407:327–339. [PubMed: 11014182]
11. Schlunzen F, Tocilj A, Zarivach R, Harms J, Gluehmann M, Janell D, Bashan A, Bartels H, Agmon I, Franceschi F, Yonath A. *Cell* 2000;102:615–623. [PubMed: 11007480]
12. Sohmen D, Harms JM, Schlünzen F, Wilson DN. *Cell* 2009;138:1248. [PubMed: 19766574]
13. Sohmen D, Harms JM, Schlünzen F, Wilson DN. *Cell* 2009;139:212. [PubMed: 19804764]
14. Ehrenberg, M. Scientific Background on the Nobel Prize in Chemistry. 2009.

Table 1

Nobel Prize awards recognizing technologies that enabled measurement science

Laureates	Year	Enabling Technologies ^a
Chemistry		
J.B. Fenn and K. Tanaka	2002	Soft desorption ionization methods for mass spectrometry
K. Wüthrich	2002	Nuclear magnetic resonance spectroscopy for determining structures of biological macromolecules in solution
K. Mullis	1993	Polymerase chain reaction
R. Ernst	1991	Methodology of high-resolution nuclear magnetic resonance spectroscopy
H. Hauptman and J. Karle	1985	Direct methods for the determination of crystal structures
A. Klug	1982	Crystallographic electron microscopy
J. Heyrovsky	1959	Polarography
A. Martin and R. Synge	1952	Partition chromatography
A. Tiselius	1948	Electrophoresis
F.W. Aston	1922	Mass spectrograph
T.W. Richards	1914	Determination of the atomic weight of chemical elements
Physics		
W. Boyle and G.E. Smith	2009	Imaging semiconductor circuit—the CCD sensor
J.L. Hall and T.W. Hänsch	2005	Laser-based precision spectroscopy, including the optical frequency comb technique
P.G. de Gennes	1991	Methods of discovering order in simple systems
G. Binnig and H. Rohrer	1986	Scanning tunneling microscope
N. Bloembergen and A.L. Schawlow	1981	Laser spectroscopy
K.M.B. Siegbahn	1981	High-resolution electron spectroscopy
F. Zernike	1953	Phase contrast method including the phase contrast microscope
C.V. Raman	1930	Raman effect
W.H. Bragg and W.L. Bragg	1915	Use of X-rays to determine crystal structure
M. Von Laue	1914	Diffraction of X-rays by crystals
A.A. Michelson	1907	Optical precision instruments and spectroscopic and metrological investigations

^aDescription of discoveries as reported by the Nobel Foundation: <http://nobelprize.org>