Alexander Rich

1924–2015

Shuguang Zhang & Burghardt Wittig

One of molecular biology's intellectual leaders, Alex Rich made fundamental discoveries concerning nucleic acids and ribosomes, which served not only as a foundation for modern biology but also spurred the field of biotechnology.

Hybridizations of nucleic acids are among the most ubiquitous and fundamental reactions in biology. Without them, DNA sequencing, RNA profiling, the polymerase chain reaction (PCR), RNA interference, genome editing and a plethora of other modern biotechnologies would not be possible. Yet, many who use these molecular biology tools may not appreciate that it was Alexander Rich, the late William Thompson Sedgwick Professor of Biophysics at the Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts, who was instrumental in their discovery. Indeed, the scientific career of Rich, who passed away on April 27, 2015, spans not only nucleic acid hybridizations but also many other trailblazing scientific discoveries and insights that provided the foundations for modern biology and spurred a host of innovations in biotech (**Box 1**).

Formative years

Rich grew up in a humble eastern European and Russian immigrant family in Hartford, Connecticut. During World War II, he attended high school by day and worked at night in an Army rifle factory (**Fig. 1**). He remarked later how he was fascinated by the barrels of the rifles—barrels reminiscent of the molecular helices of DNA, RNA, peptides and proteins, on which he would work for the rest of his life.

Shuguang Zhang is at the Center for Bits & Atoms of the Media Lab at MIT, Cambridge, Massachusetts, USA, and Burghardt Wittig is at the Foundation Institute Molecular Biology and Bioinformatics, Freie Universitaet Berlin, Berlin, Germany.
e-mail: shuguang@mit.edu or bw@zedat.fu-berlin.de

At the encouragement of his high school English teacher, he applied to and received a scholarship for tuition to Harvard College in 1942. After enlisting into the Navy V12 program and working in a submarine base hospital for 6 months, he returned to Harvard in 1946 where he completed his medical degree and later worked (and published two scientific papers) with John Edsall. Working in Edsall's laboratory, Rich had the opportunity to meet many of the era's leading scientists, including Cambridge University's J.D. Bernal (a.k.a., the "Sage"), who was the mentor of several British Nobel laureates, including Francis Crick, Max Perutz, Dorothy Hodgkin and Aaron Klug. It was on Edsall's recommendation that Rich wrote to Linus Pauling asking to work in his group. Pauling was already legendary in chemistry, to which he was the first to apply the principles of quantum mechanics, and was at the time working to determine models of protein secondary structure from X-ray diffraction analysis. This was a time when Rich not only was beginning to explore his intellectual possibilities, but also embarking on another long and happy personal journey. After completing his medical studies in 1949, he left for a trip to Europe on a trans-Atlantic ship *RMS Samaria*, where he met and courted his future wife, Jane King. They remained together for the next 63 years.

In October 1949, Rich showed up in Linus Pauling's laboratory at the California Institute of Technology (Caltech) in Pasadena, California, eager to learn. He made many lifelong friends among Pauling's team, including Martin Karplus, Matt Meselson, Gary Felsenfeld, David Davies, Leslie Orgel, Dick Marsh, Robert Shulman and especially Jack Dunitz, who patiently taught Rich the art of X-ray crystallography. The small and intimate

Figure 1 Alex Rich at 17 years old. Source: Alex Rich collection.

Caltech campus also meant that Rich mixed and became fast friends with many other scientific luminaries, such as Max Delbrück, Richard Feynman, James Watson, Benoit Mandelbrot, Carleton Gajdusek, Irwin Oppenheim, Verner Schomaker, Jerome Vinograd and Hardin McConnell.

From Caltech to Cavendish

After Rich had worked in his group for three years, Pauling suggested that Rich try to obtain X-ray patterns of DNA. At that time, because the camera was not optimal and X-ray radiation was very weak, it required a 24-h exposure to collect the DNA fiber diffraction data. After a few months of painstaking work, Rich obtained well-oriented photographs. James

Box 1 A Rich biotech heritage

Alex Rich was an early adopter of the idea of translating his discoveries into practical and commercial applications. He co-founded Repligen (Waltham, MA, USA) in 1981 and remained as chairman emeritus of the board until recently. Repligen, a reagents and materials supplier, is one of the world's premier suppliers of native and recombinant Protein A, as well as growth factors for cell lines and chromatography columns. In 1987, Rich also founded drug delivery specialist Alkermes (originally located in Cambridge, Massachusetts, now merged with Elan in Dublin). The company was founded on a sustained-release technology but has now matured into a fully integrated neurology drug developer. Among other forays into the biotech world, Rich was also a member of the board of directors of Profectus Biosciences (Baltimore). To all of these ventures, he not only brought his considerable intellect and insights but also offered an encyclopedic knowledge of the community; Rich was on close terms with a staggering number of scientists. Later, on the basis of a serendipitous discovery of self-assembling peptides found in a Z-DNA binding protein, zuotin, one of us (S.Z.) and Rich co-founded 3D Matrix (first started in Cambridge, Massachusetts, now headquartered in Tokyo), which is developing peptide biomaterials for accelerated wound healing and for surgical uses. In 1998, B.W. also founded a publicly traded German biotech, MOLOGEN (Berlin), to develop linear, covalently closed DNA-constructs (originally used to study Z-DNA formation as a function of torsional strain) into gene- and immunotherapies of cancer.

Watson later remarked at the "30 years of DNA Double-Helix Celebration" conference in Cambridge, UK, that "Alex Rich arrived at Caltech and began to take X-ray photographs at just about the time that we proposed our model. I think it was inevitable that the structure would have been solved within about a year. The momentum was there, and they really knew DNA was important"[1].

In September 1953, Pauling organized a conference on the structure of proteins and nucleic acids. A group of British scientists—Max Perutz, John Kendrew and Francis Crick from the Cavendish Laboratory in Cambridge, UK, as well as Maurice Wilkins and John Randall from King's College London—came to the meeting. It was a 'Who's Who' in protein chemistry and molecular biology in its early days (**Fig. 2**). During this conference, Crick invited Rich to Cambridge to use their rotating anode instrument for RNA diffraction, which deployed a more intense X-ray beam and required less fiber. Two years later, Rich traveled to the Cavendish laboratory, supposedly for a short visit. Soon, however, after the arrival of Leslie Orgel and James Watson, intense discussions were under way about RNA structure and the daunting problem of genetic code (**Box 2** and **Fig. 3**). Rich's initial short stay in Crick's house extended to over 6 months, and he was later joined by his wife Jane.

One Saturday morning, after Crick had read a *Nature* article over breakfast about a powder X-ray diagram and infrared spectrum of polyglycine II, Crick suggested to Rich that they build a skeletal brass molecular model of the protein polymer. By the afternoon, they had succeeded in building a model. During afternoon tea, Rich also realized that the unsolved structure of collagens had many glycine and proline or hydroxyproline residues, so the pair then started to build another model of repeating Gly-Pro-Pro. The resulting model was written up in two landmark letters to *Nature* in 1955 (refs. 2,3) and a full paper in the *Journal of Molecular Biology* in 1961 (ref. 4). In 1995, 40 years after their short letters, Helen Berman's laboratory reported the single-crystal structure of collagen. It turns out that this fits the Rich-Crick collagen model very well[5]. We now know that 28 types of collagens comprise ~30% of proteins in the human body. Collagen has been widely used for cosmetics and tissue repairs and recombinant collagens have been produced on a large scale. Because of his work on the structures of polyglycine II and collagen, Rich was recruited as a scientific advisor by DuPont (Wilmington, DE, USA), a role he fulfilled for over a decade.

Later, the Riches opened their house in Cambridge, Massachusetts, to the Crick family and a seemingly never-ending stream of scientists and interesting personages from around the world.

As Rich often remarked, in science, when you look back, everything is sunny and clear and some people even wonder why it took so long to make such discoveries; but when you look ahead, many things are in the fog and hard to navigate.

After the DNA double helix structure was solved in outline through model building and low-resolution fiber X-ray diffraction in 1953, the questions that remained in the fog were, Would RNA form a double helix? Would DNA-RNA form a double helix? And how does DNA make RNA? In their short *Nature* letter on the DNA double helix, Watson and Crick specifically pointed out, "[It is] probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact."

Figure 2 The conference on the structures of proteins and nucleic acids at Caltech, Pasadena, Calif., which took place from the 21st to 25th of September, 1953, where Rich first met Crick. Rich is second from the left in the second row. Source: Alex Rich collection.

Molecular sex at NIH

By 1952, Rich's fellowship from the US National Research Council was coming to an end, and he was appointed by Seymour Kety, then organizing research groups for the newly formed National Institute of Mental Health (of the US National Institutes of Health (NIH)), to be head of the section on physical chemistry. After arriving at NIH in mid-1954, Rich set about recruiting top researchers—including his Caltech colleague Dunitz—and began a series of investigations using poly-riboadenylic acid (poly-rA) and poly-ribouridylic acid (poly-rU) to address these fundamental questions about RNA. In the spring of 1956, Rich started experiments with David Davies (another former Caltech colleague) mixing together poly-rA and poly-rU. To their astonishment, when the RNAs were mixed, they noted that the solution immediately became viscous. And when the resulting RNA fiber was analyzed by X-ray diffraction, the pattern was comparable to that of DNA. When Rich excitedly told one of his biochemist colleagues at NIH the results of his experiment, it was met with disbelief. "Without an enzyme?" his colleague asked incredulously; in the 1950s, it was inconceivable that two different complex biopolymers could combine into a single double helix without enzyme catalysis.

Rich had nevertheless discovered the first hybridization reaction—or "molecular sex," as British journalist Julian Huxley called it. It represented a paradigm shift in the way chemists and biochemists thought about interactions between macromolecular nucleic acids[6]. Hybridization is the basis for all DNA-DNA, RNA-RNA, DNA-RNA complementary recognitions and all the resulting technologies in the molecular biology tool box (e.g., microarrays, antisense, RNAi, PCR and CRISPR-Cas9, to name a few). The DNA-RNA pairing also immediately suggests the genetic information transfer from DNA to RNA, namely transcription.

Exploring RNAs at MIT

By 1958, Rich had accepted a position at MIT. After the discovery of mRNA, one big question in the following years was how RNA makes proteins. The deciphering of the genetic code was underway thanks to the efforts of Marshall Nirenberg at the NIH using a cell-free system and poly-rU, poly r-AU and poly-rA. Crick and Sydney Brenner had already determined that each codon has three nucleotides by using bacterial phage genetics and proposed the adopter hypothesis (which turned out to be tRNA). But the question of how RNA made protein remained unclear.

Rich asked his first graduate student, Jonathan Warner, to see if there were several ribosomes associated with each mRNA. They soon discovered that proteins are made not by single ribosomes, but by polyribosomes, namely, each mRNA allows several ribosomes on it, like many train cars on a railroad track, to make proteins most efficiently and rapidly. In 1962, Rich submitted two papers, one reporting the electron microscopy studies, the other reporting the biochemical experiments using sucrose density gradient sedimentation and isotope tracing. After the first electron microscopy paper was published in *Science*[7], it was greeted with great skepticism, until the second paper[8] came out in the following month, and several other laboratories confirmed their findings.

After the polyribosome discovery, Rich asked how the amino acids were joined inside the ribosome. Using rabbit reticulocyte cells (which have no nucleus and no longer synthesize RNA), they were able to do a clean analysis of the system by incubating the reticulocytes with radioactive adenine or cytosine. These nucleotides could penetrate into the interior, where they were incorporated into ribonucleoside-triphosphates. Although RNA was not synthesized, the 5′ CCA ends of tRNA molecules were continually cleaved off and then enzymatically reattached to tRNA. The radioactive nucleotides thus labeled the ends of tRNA molecules and nothing else. This showed that two tRNA molecules were bound to active ribosomes, but only one was bound to inactive ribosomes at the top of the gradient. Rich and his colleagues postulated that the two tRNA-binding sites occupy adjacent codons. They called one 'Site A', which bound aminoacyl-tRNA, and the other 'Site P', which bound peptidyl-tRNA. Their idea was that these two sites acted in a coordinated manner to transfer the growing polypeptide chain and to move the mRNA codon from Site A to Site P. In addition, they suggested that it constituted the basis of ribosomal movement relative to the mRNA strand. When the crystal structure of the ribosome was finally determined 37 years later, it was revealed that the ribosome indeed has an A site and a P site (as well as an exit 'E site'). Rich's laboratory also discovered the ~10-nm ribosome tunnel where the newly synthesized polypeptide chains exit the ribosome. This tunnel turns out to be the point where many antibiotics exert their action through 'molecular constipation'.

After tRNA was identified in the 1960s, efforts were redoubled to attempt to obtain single crystals of tRNA; although methods for purifying tRNA continued to improve, good-quality tRNA crystals continued to remain elusive. In 1968, however, Sung-Hou Kim in the Rich laboratory obtained single crystals of *Escherichia coli* $tRNA^{fMet}$. At the same time, three other groups also obtained single tRNA crystals diffraction but all with limited

Box 2 The RNA Tie Club

Alex Rich was one of 20 members of the RNA Tie Club (**Fig. 3**). Each member represented an amino acid. Rich was arginine (for his initials A.R.) and the club's Lord Privy Seal of the British Cabinet. The physicist George Gamov was alanine (as the Ala) and Jim Watson, proline (as the Pro). The RNA Tie Club was organized as a practical joke by Gamov (who also coined the term "Big Bang" of the universe and proposed that the genetic code comprises three letters). As well as recruiting other biologists, such as Sidney Brenner (Val), Paul Doty (Asp), Norman Simons (Iso) and Harold Gordon (Ser), the club included physicists Richard Feynman (Gly), Edward Teller (Leu), Max Delbrück (Trp), Marvin Calvin (His), Francis Crick (Tyr), Leslie Orgel (Thr), Gunther Stent (Phe) and Erwin Chargaff (Lys). The group never really met as a whole but did its work circulating ideas through manuscripts. Indeed, Crick used the club to gain feedback on his RNA adopter hypothesis, which ultimately turned out to be identified as tRNA.

Figure 3 Four not-so obscure members of the RNA Tie Club displaying natty neckwear in Francis Crick's home 'The Golden Helix' in Cambridge, UK, 1955. From left, Francis Crick, Alex Rich, Leslie Orgel and Jim Watson. Source: Alex Rich collection.

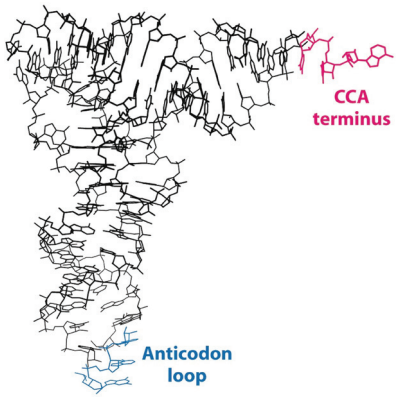

Figure 4 The structure of tRNA. The fold of yeast tRNAphe at 3-Å resolution that revealed the complete interactions of L-shaped molecule as shown on the cover of *Science*[9]. The L-shaped tRNA molecule is now a standard feature of molecular biology, having been found in virtually all tRNA molecules, even when they are complexed to aminoacyl synthetase enzymes. The significance of the folding is twofold. First, it revealed that the 3′ acceptor end is over 70 Å away from the anticodon loop, which has implications for understanding the interaction between tRNA molecules and tRNA aminoacyl synthetases. Second and most important, it suggested that the interaction of the tRNA molecules with mRNA occurs at one end of the L, whereas the segment responsible for forming the peptide bond is considerably removed from the site. This makes it possible to have great specificity with many interactions at either end of the molecule due to this separation.

resolution. After numerous failures, in 1971, the Rich laboratory reached an exciting turning point—yeast $tRNA^{phe}$ could be crystallized in a simple orthorhombic unit cell with a resolution of 2.3 Å! These were the first crystals of tRNA suitable for detailed structural analysis. The key event in making these crystals was the incorporation of spermine, a naturally occurring polyamine. It was found later that the spermines were bound specifically to yeast $tRNA^{phe}$ and stabilized it so that it made a high-resolution crystal—an important innovation in crystal stabilization protocols at the time.

The L-shaped folding of the tRNA polynucleotide chain at 4-Å resolution was a dramatic and surprising discovery, as was the separation between the acceptor site and the anti-codon. The backbone tracing (**Fig. 4**) was published on the front page of The *New York Times* on January 13, 1973, together with a discussion of its role in protein synthesis. No one had anticipated that the molecule would organize itself in this fashion. This folding was compatible with much of the biochemical experimental data concerning tRNA molecules. The final high-resolution structure was published in 1974 jointly with Kim's group, who had moved to Duke University in 1972 (ref. 9). The tRNA structure further confirmed Watson-Crick base pairing and also revealed numerous non-Watson-Crick base pairs and base triplets that, some 20 years later, were found in many ribozymes and in the RNA folds of ribosomes. The detailed tRNA structure and its complex interactions have stood the test of time.

Double-helix structures

By the early 1970s, Rich's laboratory was turning its focus to the pursuit of high-resolution structures using single-crystal X-ray diffraction. Single-crystal growth was extremely difficult at that time; everything was done by trial and error, and each step took a very long time to accomplish. Finally in 1973, John Rosenberg and Ned Seeman and others in the Rich laboratory succeeded in determining the structure of r-GpC and r-ApU at 0.8-Å resolution.

What did such a high-resolution structure mean for our understanding of nucleic acid base pairing? The GpC structure had the anticipated base pairs connected by three hydrogen bonds. However, the ApU structure showed for the first time that Watson-Crick base pairs formed when the molecule was constrained in a double helix, as opposed to the Hoogsteen base pairs that were favored in the single-crystal complexes of adenine with uracil derivatives. Rich mailed preprints of the paper[10] to several people, including Jim Watson, who soon telephoned Rich, saying that the ApU manuscript had finally dispelled any uncertainty he had about the organization of the double helix—and that, after 20 years, he could finally get his first good night's sleep! The significance of the double helix at atomic resolution was recognized in a News and Views commentary[11], which called it the "missing link" and recognized that "the many pearls offered" helped resolve one of the big uncertainties in nucleic acid structure.

Rich was keenly aware that new methods and new technologies could accelerate scientific discoveries and change the way people did science. As soon as DNA nucleotide synthesis became available, he collaborated with Jacques Van Boom of the University of Leiden in the Netherlands, who synthesized and provided large quantities of oligo DNA d(CGCGCG). Using this oligo DNA, Andy Wang in the Rich laboratory obtained crystals that diffracted to 0.9-Å resolution, with every atom clearly visible. Heavy atoms were used to solve the structure, which revealed, remarkably, a left-handed double helix with two antiparallel chains held together by Watson-Crick base pairs. Every other base had rotated around the glycosyl bonds so that the bases alternated in anti- and syn- conformations along the chain. The zigzag arrangement of the backbone (hence, Z-DNA) was different from the smooth, continuous coil seen in B-DNA (**Fig. 5**). The general response to this unusual structure was amazement, coupled with skepticism. When Rich telephoned Crick to report to him the unexpected finding of the left-handed double helix at 0.9-Å resolution, there was a long silence at the other side of the line. Rich then assured Crick that this may be a special case because it has a repeating d(CGCGCG) and some resulting special features.

The Z-DNA discovery generated excitement for physical and structural chemists as well as for structural biologists, but many biologists were skeptical. It has been demonstrated that Z-DNA can be generated by negative supercoiling that is produced during DNA unwinding and gene transcription and recombination. Thus, Z-DNA requires higher energy to stabilize it, and its formation is transient and dynamic. It has also been found that many potential Z-DNA-forming sequences reside near the transcription start sites. Rich had a conviction that if there were alternative DNA conformations, nature would exploit them because evolution is opportunistic.

Elucidating a biological role for Z-DNA turned out to be a long and painstaking pursuit[12]. Rich's laboratory, in collaboration with others, developed a Z-DNA-specific monoclonal antibody that was used to probe for Z-DNA in the genome. These studies demonstrated that

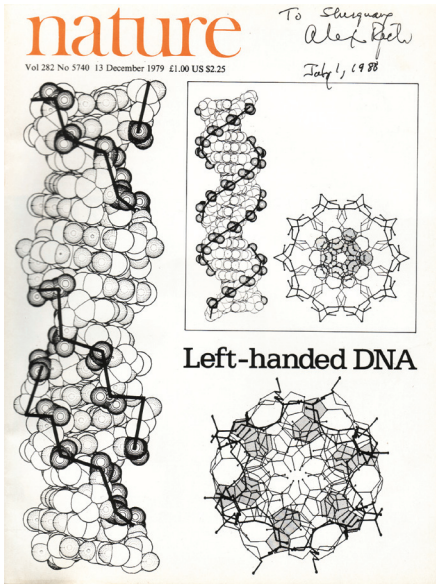

Figure 5 The cover of 13 December issue of *Nature* in 1979 displaying the structure of Z-DNA. The illustration shows a comparison between B-DNA and Z-DNA, with solid lines running from phosphate to phosphate.

Z-DNA conformation often resides in transcriptionally active, rather than silent, genes, suggesting that Z-DNA has a biological role. One of us (B.W.) used a UV laser pulse method to crosslink the Z-DNA-specific monoclonal antibody to specific DNA segments in the genome and identify regions where Z-DNA might be present. As it turned out, Z-DNA is found on three upstream regions of the *c-MYC* oncogene.

As in the 1960s and 1970s, when Rich energized students and postdocs to crystallize tRNAs, after Z-DNA's description in 1979, Rich energized people to discover and purify Z-DNA binding proteins from various cells. There were numerous and spectacular failures, and many people could not find proteins. But as Rich often repeated, "Persistence is luck." One of us (S.Z.) found a putative Z-DNA binding protein, called zuotin in yeast after many such failures. Alan Herbert also spent many years developing an affinity Z-DNA binding assay using 20,000-fold excess of B-DNA and single-stranded DNA. Using this approach, he finally identified and purified a Z-DNA binding protein called ADAR1, an RNA-specific adenosine deaminase involved in RNA editing. Thomas Schwartz and others later determined the co-crystal structure of d(CGCGCG) and the 70-amino-acid Z-DNA binding fragment of ADAR1, called $Z\alpha_{ADAR1}$ at 2.1-Å resolution, revealing how the $Z\alpha_{ADAR1}$ protein binds to Z-DNA, and how it can be used to search for homologs of $Z\alpha_{ADAR1}$. Using this approach, the Rich laboratory found other Z-DNA binding proteins. One is called DLM1, which is upregulated in tissue in contact with tumors and is also induced by interferon. The 1.85-Å resolution co-crystal structure of a domain of DLM1 ($Z\alpha_{DLM1}$) with d(CGCGCG) showed that the DNA-binding feature is very similar to that of $Z\alpha_{ADAR1}$ but with minor variations. Another such Z-DNA binding protein is E3L, which was found in DNA poxviruses including vaccinia. An interesting biological observation arising from this work was that the lethal action of injected wild-type of vaccinia virus in mice can be abrogated by mutating and/or deleting the Z-DNA binding residues of ZaE3L.

Polymath and humanist

Rich was not only a deep thinker and great scientist with many interests, but he was also a caring humanist, with an open heart and open mind (**Box 3** and **Fig. 6**). He participated in an advisory role to David Ben-Gurion in establishing the Weizmann Institute of Sciences in Israel during the 1950s. He traveled tirelessly to Israel many times, both alone and with his family and served as a member of the Weizmann Institute's governing board from its inception until recently.

During the peak of the Cold War, Rich traveled to the Soviet Union and befriended many leading Soviet scientists. Such interactions, though unpopular with many politicians at home, served to reduce tensions between the United States and the Soviet Union. Rich also went to China in 1973 and discussed tRNA with leading Chinese scientists. Inspired by his visit, Chinese scientists made the first chemical synthesis of tRNA in the 1970s. Rich also was instrumental in establishing the early relationship between the US National Academy of Sciences and the Chinese Academy of Sciences (Beijing). He was a tireless traveler and gave keynote addresses, lectures and short courses around the world.

As a result of his scientific excellence and stature in molecular biology, he received many honors and awards, including the US National Medal of Science, the Welch Award in Chemistry, the Bower Award of the Franklin Institute and the Lomonosov Gold Medal of the Russian Academy of Science. He was elected to all major scientific academies, including the Pontifical Academy of Science (in the Vatican, where he helped to advise the Pope for decades), the US National Academy of Sciences, the French Academy of Science and the Russian Academy of Sciences. He received numerous honorary doctorates. However, these honors never inflated his ego or affected his sense of purpose or intense interest in the latest discoveries across various disciplines. Until his last days, he was often very excited about the latest discoveries. Typical of Rich, these interests were spread over a many disciplines, including microbiome transplants, unnatural nucleobases (e.g., d5SICS and dNaM), CRISPR-Cas9 for genome editing as well as the discovery of water on Jupiter's

Box 3 Beyond molecular biology

Figure 6 A scientific meeting in Moscow, then the Soviet Union, at the height of the Cold War. From left, Alexander Rich, Linus Pauling, and several unidentified Russian scientists. Source: Alex Rich collection.

Beginning in the 1950s, Alex Rich was a very active humanist, aiming to bring an end to the cold war. With John Edsall, Linus Pauling and other leading scientists, he actively participated in the Pugwash Conferences on Science and World Affairs with leading scientists from the Soviet Union, China and other countries. One of the key figures of the humanist movement Rich met early in his career was Albert Einstein; indeed, after shaking Einstein's hand on his first meeting, Rich went so far as to wrap his right hand with a cloth bandage, which he only later took off in front of his brother David, saying "I want you to be the first to shake the hand that shook the hand of Einstein."

The conferences of the Pugwash movement, which was ultimately awarded the Nobel Peace Prize in 1995, served as useful forums for exchanging and discussing ideas and helped to minimize tensions then growing between the East and West. At a meeting in Moscow in 1960, Rich met several scientists from the Soviet Union (**Fig. 6**). Rich often wrote joint papers with the Soviet scientists attending Pugwash meetings, presenting suggestions on alleviating tensions in the nuclear arms race. At a meeting in London in 1962, a Russian colleague and Rich developed the idea that they might use automated seismographs to monitor nuclear testing—so-called black boxes. The proposal was then signed by several other American and Soviet scientists and became a document of the conference, which was subsequently sent to world leaders. At one stage, the Soviet Union contemplated using such automated seismographs, and it was one of the elements that facilitated the eventual signing of the Limited Test Ban Agreement in 1963. Although such conferences took an enormous amount of time, Rich considered his effort worthwhile because it addressed a major problem facing the world—the possibility of nuclear war.

moon Ganymede and on Saturn's moon Enceladus.

Indeed, Rich's interests and curiosity reached beyond terrestrial biology and out to the stars. He was deeply involved in the space program to search for extraterrestrial life, for which he was honored with the Theodore von Karmen Award for the Viking Mars mission and the Skylab Achievement Award of the National Aeronautics and Space Administration. He had a keen interest in the timeless question of the origin of chemical life in the universe and published speculative papers in this area.

Rich was a great storyteller and enjoyed recounting the high suspense accompanying many of his scientific discoveries. He always captivated his audiences from near and far with personal stories, sometimes scientific, but oftentimes not. He loved meeting interesting people of all ages from all walks of life and collecting friends. He had a very warm personality that naturally attracted people to him. His sound and frank advice was widely sought by people from all social strata. He loved to take long walks with people and have animated talks. Everyone enjoyed walking and talking with him on all sorts of topics—anything that came to his mind.

More than anything, one saw in Rich an original curiosity working. He was generous with his ideas and often stimulated others' imaginations—others would say he carelessly gave out his ideas. One wonders why he made so many important discoveries throughout his life. His laboratory was always a microcosm of people from all backgrounds. He not only opened his laboratory to all kinds of people including artists, like Joe Davis, but he also invited people to his home for meals at a moment's notice. The parties on every occasion in his home were legendary, gathering a great mix of interesting people. One invariably found someone interesting to talk to.

If one can attempt to sum up Rich's personality in one word, it would be open-mindedness. This quality opened the entire world, not only for him, but also for everyone around him.

ACKNOWLEDGMENTS

We thank S.-H. Kim and J. Rich for their input. Part of this obituary is adapted from Alex Rich's autobiography[13].

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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