Prof. Alexander Rich
William Thompson Sedgwick Professor, Department of Biology, MIT

Most important awards, prizes and academies

Awards: Sigma Xi Proctor Prize, Raleigh, NC (2001); Bower Award and Prize, the Franklin Institute, Philadelphia, PA (2000); National Medal of Science, Washington, DC (1995); Linus Pauling Medal, American Chemical Society, Northwest Sections (1995); Lewis S. Rosenstiel Award in Basic Biomedical Research, Brandeis Univ., Waltham, MA (1983); James R. Killian Faculty Achievement Award, Massachusetts Institute of Technology (1980); Presidential Award, New York Academy of Science, New York, NY (1977); Theodore van Karmen Award for Viking Mars Mission, Washington, DC (1976); Skylab Achievement Award, National Aeronautics and Space Administration, Washington, DC (1974). *Academies*: Foreign Member, Russian Academy of Sciences, Moscow, Russia (1994); Honorary Member, Japanese Biochemical Society, Tokyo, Japan (1986); Foreign Member, French Academy of Sciences, Paris, France (1984); Honorary Doctorate, Federal University of Rio de Janeiro, Brazil (1981); American Philosophical Society, Philadelphia, PA (1980); Pontifical Academy of Sciences (1978); National Academy of Sciences, Washington, DC (1970); Fellow, American Association for the Advancement of Science, Washington, DC (1965); Fellow, Guggenheim Foundation (1963); Fellow, American Academy of Arts and Sciences, Boston, MA (1959); Fellow, National Research Council, Washington, DC

(1949-51).

Summary of scientific research

The central thrust of my research has been an attempt to understand the relationship between molecular structure and biological function especially of nucleic acids and proteins. While working as a postdoctoral fellow with Linus Pauling at Caltech, I was strongly impressed with the power of x-ray diffraction analysis in defining structure. Some of my earlier work at the time concerned the then unknown structure and function of ribonucleic acid. In the mid 50s, I studied the structure of natural and synthetic polynucleotides using fiber x-ray diffraction. A variety of different helical molecules were discovered containing two, three or four strands. These studies were later complemented by using single crystal x-ray diffraction analysis with purine-pyramidine intermolecular complexes. These demonstrated the wide variety of hydrogen bonding interactions of nucleic acid bases. Some of my earlier work concerned the structure of polypeptides. We determined the structure of polyglycine-II, a molecule which contains a unique hydrogen bonding system. This served as a clue for our discovering the structure of collagen, the fibrous protein of skin and connective tissue. In the early 1960s great interest was associated with the role of messenger RNA in protein synthesis. By its length, it seemed apparent to me that messenger RNA was long enough to associate simultaneously with several ribosomes while it was being translated. Out of this we discovered polyribosomes and carried out a series of studies dealing with the nature of the polyribosomal protein synthetic system. This led to a detailed analysis of events in the ribosome and the role of transfer RNA. In the late 60s we discovered we could crystallize pure species of transfer RNA. Solution of its three-dimensional structure by x-ray diffraction would produce information to help understand its mode of action in protein synthesis. Crystals were discovered that diffracted to high resolution and by 1973 we had traced the chain of yeast phenylalanine tRNA. In 1974 at 3 Å resolution we could discern the entire structure. It was an unusual structure, bent so that one end interacts with the messenger RNA during protein synthesis while the other end 75 Å away has the amino acid attached. We continue to address the problem of how this molecule works. In 1979 we solved the structure of a fragment of RNA that was found to be in a novel left-handed form. This conformation of the double helix, called Z-DNA, is a high energy form of the more familiar right-handed helix. For several years we have studied both its chemistry and biology. We now know which forces inside the cell act to stabilize Z-DNA and we understand a great deal about its conformation. A class of proteins were discovered that bind specifically to Z-DNA, many in regulatory regions. Co-crystallization of these proteins with Z-DNA has led to an understanding of how Z-DNA is recognized. In turn, this has led to other biological activities.

Main publications

Rich, A. (with Crick, F.H.C.), The Structure of Collagen, *Nature*, 176, pp. 915-6 (1955); Rich, A. (with Davies, D.R.), A New Two-Stranded Helical Structure: Polyadenylic Acid and Polyuridylic Acid, *J. Amer. Chem. Soc.*, 78, p. 3548 (1956); Rich, A. (with Felsenfeld, G. and Davies, D.R.),

Formation of a Three-Stranded Polynucleotide Molecule, *J. Amer. Chem. Soc.*, 79, pp. 2023-4 (1957); Rich, A., A Hybrid Helix Containing Both Deoxyribose and Ribose Polynucleotides and its relation to the Transfer of Information Between the Nucleic Acids, *Proc. Nat. Acad. Sci. USA*, 46, pp. 1044-53 (1960); Rich, A. (with Davies, D.R., Crick, F.H.C. and Watson, J.D.), The Molecular Structure of Polyadenylic Acid, *J. Molec. Bio.*, pp. 71-86 (1961); Rich, A. (with Warner, J.R. and Knopf, P.M.), A Multiple Ribosomal Structure in Protein Synthesis, *Proc. Nat. Acad. Sci. USA*, 49, pp. 122-9 (1963); Rich, A. (with Warner, J.R. and Goodman, H.M.), The Structure and Function of Polyribosomes, *Cold Spring Harbor Symposium*, 28, pp. 269-85 (1963); Rich, A. (with Kim, S.H., Quigley, G.J., Suddath, F.L., McPherson, A., Sneden, D., Kim, J.J. and Weinzierl, J.), Three-Dimensional Structure of Yeast Phenylalanine Transfer RNA: Folding of the Polynucleotide Chain, *Science*, 179, pp. 285-8 (1973); Rich, A. (with Kim, S.H., Suddath, F.L., Quigley, G.J., McPherson, A., Kim, J.J., Sussman, J.L., Wang, A.H.-J. and Seeman, N.C.), Three-Dimensional Tertiary Structure of Yeast Phenylalanine Transfer RNA, *Science*, 185, pp. 435-9 (1974); Rich, A. (with Wang, A.H.-J., Quigley, G.J., Kolpak, F.J., Crawford, J.L., van Boom, J.H. and van der Marel, G.), Molecular Structure of a Left-Handed Double Helical DNA Fragment at Atomic Resolution, *Nature*, 282, pp. 680-6 (1979); Rich, A. (with Wittig, B., Wölfl, S., Dorbic, T. and Vahrson, W.), Transcription of Human c-myc in Permeabilized Nuclei is Associated with Formation of Z-DNA in Three Discrete Regions of the Gene, *Embo J.*, 11, pp. 4653-63 (1992); Rich, A. (with Su, L., Chan, L., Egli, M. and Berger, J.M.), A Minor Groove RNA Triplex in the Crystal Structure of a Viral Pseudoknot Involved in Ribosomal Frameshifting, *Nature Structural Biology*, 6, pp. 285-92 (1999); Rich, A. (with Schwartz, T., Rould, M.A., Lowenhaupt, K. and Herbert, A.), Crystal Structure of the Zα Domain of the Human Editing Enzyme ADAR1 Bound to Left-Handed Z-DNA, *Science*, 284, pp. 1841-5 (1999); Brown, B.A., II, Lowenhaupt, K., Wilbert, C.M., Hanlon, E.B., and Rich, A., The Zα domain of the editing enzyme dsRNA adenosine deaminase binds left-handed Z-RNA as well as Z-DNA, *Proc. Nat'l. Acad. Sci. USA*, 97: 13531-86 (2000); Kim, Y.-G., Lowenhaupt, K., Maas, S., Herbert, A., Schwartz, T. and Rich, A., The Zab domain of the human RNA editing enzyme ADAR1 recognizes Z-DNA when surrounded by B-DNA, *J. Biol. Chem.* 275: 26828-33 (2000).

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