Sidney Altman

1939-2022

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
by Daniel DiMaio

NATIONAL ACADEMY OF SCIENCES

SIDNEY **ALTMAN**

May 7, 1939–April 5, 2022

Elected to the NAS, 1990

Photograph by Michael Marsland

By Daniel DiMaio

Sidney Altman was a molecular biologist who fundamentally changed our understanding of basic biological processes. In recognition of his unexpected and initially controversial discovery that RNA could function as an enzyme, he shared the 1989 Nobel Prize in Chemistry with Thomas Cech. Until the 1980s, it was a truth universally acknowledged that only proteins could function as enzymes and that the primary role of RNA—formalized as Crick's Central Dogma—was to convert the genetic information encoded in DNA into proteins that perform the biochemical reactions in cells. RNA serves as messengers (mRNAs) that carry the genetic instructions from the genes to the ribosomes and as small adaptor molecules (tRNAs) that translate the sequence of bases in the mRNA into the amino acid sequence of proteins according to the genetic code. The ribosomes themselves are composed of 50 or more proteins associated with a few RNA molecules (rRNAs), which were thought to provide a largely inert scaffold to support the action of the proteins that catalyze peptide bond formation during protein synthesis. Admittedly, the genomes of some viruses consist of RNA, showing that DNA does not have an exclusive monopoly on storing and transmitting genetic information, but catalyzing biochemical reactions inside cells was thought to be the sole province of proteins. The great discovery that RNA molecules could be enzymes upended this view and revealed an important new biological principle that, in the words of the Nobel Prize announcement, "altered the central dogma of the biosciences."

Sid Altman was born in Montreal, Canada, on May 7, 1939, the son of Jewish immigrant parents from Poland and Ukraine. His father had worked as a laborer on a collective farm in Ontario until he purchased and ran a small grocery store in Montreal. His mother worked in a textile mill prior to her marriage. Although Sid characterized his family as poor and neither of his parents graduated from high school, they valued education. Sid's interest in science was sparked as a young child by his fascination with the atomic bomb and later by the elegance and predictive power of the periodic table of

the elements, which he first saw in a book given to him when he was thirteen years old. Albert Einstein was held up to him as a worthy role model.

Sid attended the Massachusetts Institute of Technology (MIT), where he studied nuclear physics and, like any good Canadian, played varsity ice hockey. He conducted his senior thesis research on electron decay with Lee Grodzins, and throughout his life, Sid credited Grodzins for inspiring him to consider science as a career. After graduation, he entered a Ph.D. program in physics at Columbia University, but his interest in this field soon waned, and he left Columbia without receiving a degree. Intrigued by an undergraduate molecular biology course taught by Cy Levinthal at MIT, he decided to pursue a Ph.D. in biophysics instead. At the suggestion of George Gamow, whom he met at a party, he joined Leonard Lerman's laboratory, initially at the University of Colorado Medical Center in Denver and later at Vanderbilt University. With Lerman, Sid shared a lab with a young student named Tom Maniatis, who later achieved renown as a pioneer during the early days of molecular cloning. For his dissertation research, Sid studied the effects of acridine dyes on the replication of bacteriophage T4 DNA at a time when phage research was revolutionizing our understanding of the molecular basis of life.[1] After completing his degree in 1967, he moved to Harvard University for a postdoctoral fellowship with Matthew Meselson and conducted studies on an endonuclease involved in bacteriophage T4 DNA replication and recombination.[2] After two years with Meselson, Sid, like many of his contemporaries in molecular biology, made the pilgrimage to the Medical Research Council Laboratory of Molecular Biology (LMB) in Cambridge, England. There, he came under the spell of Sydney Brenner, Francis Crick, and the other phage biologists whose discoveries were rewriting the textbooks.

At the LMB, which he called "scientific heaven," Sid began his studies of tRNA. He first isolated and analyzed *Escherichia coli* strains containing acridine-induced mutations that affected the activity of $tRNA^{Tyr}$, which inserted tyrosine into proteins during translation at the ribosome.[3] These studies revealed that $tRNA^{Tyr}$ was initially synthesized as a larger precursor RNA that had to be processed to become competent for amino acid acylation. Sid and John Smith isolated and characterized tRNA precursors and used the RNA sequencing methods developed by Fred Sanger at the LMB to show that the precursor molecule contained a 5' extension that was absent from the mature tRNA.[4] (Figure 1) With Hugh Robertson and Smith, Sid identified an activity in crude bacterial cell extracts that catalyzed the removal of this 5' "leader sequence" from the precursor tRNA.[5] Even though the pure enzyme was not yet in hand, they named this processing activity RNase P (P for precursor). In the first paper describing RNase P activity, published

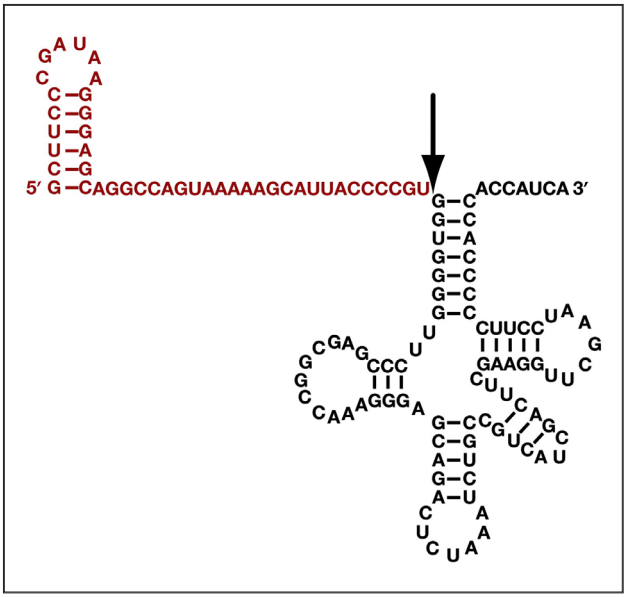

Figure 1: Diagram of $tRNA^{Tyr}$ precursor. The 5′ leader sequence removed by RNase P is shown in red, with the cleavage site indicated by the arrow. (From W. H. McClain, L. B. Lai, V. Gopalan, Trials, travails and triumphs: an account of RNA catalysis in RNase P. *J Mol Biol* 397, 627-646 (2010).

in 1972, they noted that the behavior of RNase P activity during fractionation suggested that "it is possible that the active form of RNase P…could be associated with some nucleic acid."

After Sid set up his lab as a new assistant professor at Yale University in 1971, he continued his studies of the cleavage reaction catalyzed by RNase P. For years, he conducted painstaking biochemical and genetics experiments to identify, purify, and characterize RNase P. In the course of this work, he made a series of astounding discoveries, culminating in the discovery of the first true RNA enzyme.

Sid and his team first undertook the difficult task of purifying RNase P to homogeneity. They employed classic ammonium sulfate precipitation and column chromatography methods used to purify typical proteins, but RNase P did not behave like a typical protein. The high buoyant density of RNase P observed during density gradient centrifugation suggested that the protein was associated with RNA, a denser molecule than protein. Furthermore, RNase P activity invariably copurified with specific RNA molecules, first thought to be contaminants. Ultimately, they showed that pure RNase P from *E. coli* consists of a 119 amino acid protein named C5 and a 377 base RNA named M1. The idea that an enzyme had both a protein and an RNA component encountered resistance from other biochemists, but this finding should not have been shocking. After all, it was well established at that time that ribosomes also contained both types of molecules, although the ribosomal proteins were assumed to catalyze peptide bond formation. But in 1978, Sid and his graduate student Ben Stark discovered that activity was abolished by

treating RNase P with ribonucleases, enzymes that degrade RNA.[6] (Figure 2) This experiment was technically challenging because a nuclease would also degrade the precursor tRNA substrate used to assay RNase P activity. Peter Rae, a member of Stark's thesis committee, made the key suggestion to use micrococcal nuclease, a calcium-dependent enzyme that could be inactivated prior to the addition of the precursor tRNA substrate by dialyzing out calcium, which was not required by RNase P.[7,8] The sensitivity of RNase P to nuclease digestion demonstrated that the RNA moiety of RNase P was required for activity. (Activity was also eliminated by treatment with proteases because under the low-magnesium conditions used, which presumably mimicked the situation in living *E. coli*, both the RNA and the protein components of RNase P were required for catalysis.) The report that RNase P required RNA engendered considerable criticism from scientists unwilling to believe that RNA could contribute to enzymatic activity, even though at this time Sid did not argue that RNA directly participated in catalysis. In fact, the paper by Stark and his coauthors states parenthetically that "the nucleolytic activity of the enzyme is reserved for the protein moiety."

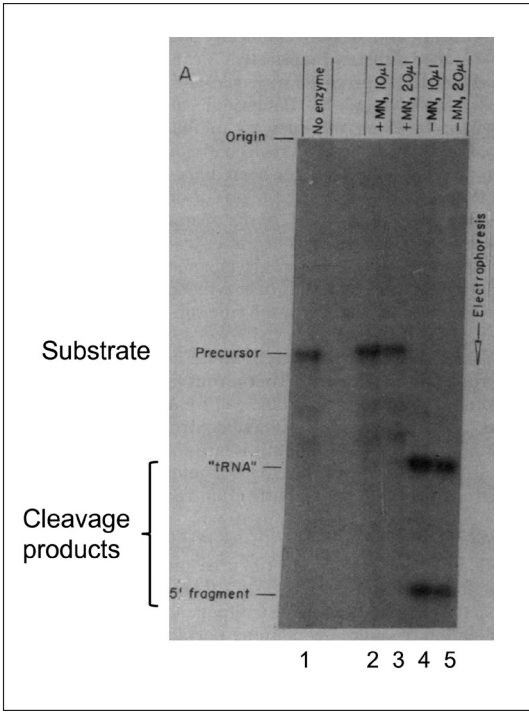

Figure 2: Autoradiogram showing that E. coli RNase P cleavage activity is inactivated by addition of micrococcal nuclease (MN) in lanes 2 and 3. (Modified from B. C. Stark, R. Kole, E. J. Bowman, S. Altman, Ribonuclease P: an enzyme with an essential RNA component. *Proc Natl Acad Sci U S A* 75, 3717-3721 (1978).

In 1979, Sid and his postdoctoral fellow Ryszard Kole isolated highly purified preparations of RNA and protein from RNase P. These preparations were inactive *in vitro* when assayed individually, but RNase P activity was reconstituted when the RNA and protein were mixed.[9] This result provided additional evidence that both RNA and protein were required for RNase P activity. Then, Norman Pace and his student Katheleen Gardiner, at National Jewish Hospital in Denver, reported that RNase P from *Bacillus subtilis*, a divergent Gram-positive bacterium, also contained an essential RNA component and could be reconstituted from inactive RNA and protein subunits, providing welcome

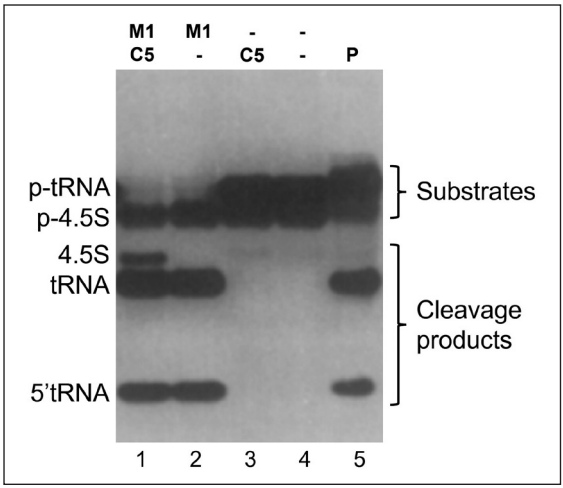

Figure 3: Autoradiogram showing that E. coli RNase P RNA subunit M1 is sufficient for cleavage of a tRNA precursor in 60 mM magnesium (lane 2), while the protein subunit C5 is inactive (lane 3). The components of RNase P added to the reaction are indicated at the top: M1, M1 RNA; C5, C5 protein; P, complete RNase P. The bands are identified on the left: p-tRNA, $tRNA^{Tyr}$ precursor; p-4.5S, 4.5S RNA precursor; 4.5S, mature 4.5S RNA; tRNA, mature $tRNA^{Tyr}$; 5'tRNA, cleaved 5' leader sequence. (Modified from C. Guerrier-Takada, K. Gardiner, T. Marsh, N. Pace, S. Altman, The RNA moiety of ribonuclease P is the catalytic subunit of the enzyme. *Cell* 35, 849-857 (1983).

confirmation of Sid's findings.[10] In 1980, Kole isolated the RNase P RNA (by then known as M1 RNA) from an *E. coli* mutant with a temperature-sensitive defect in tRNA processing and then showed that RNase P reconstituted from this RNA and the wild-type C5 protein displayed temperature-sensitive activity in an *in vitro* reaction.[11] This clever combination of genetics and biochemistry demonstrated that RNA could regulate for the activity of RNase P in vivo. Heinz Fraenkel-Conrat and Beatrice Singer had used essentially the same experimental design in the 1950s to show that RNA was the active genetic component of tobacco mosaic virus, the first evidence that genes could consist of RNA.[12]

Convinced by this accumulating body of evidence, Sid finally took the plunge in 1981. In a paper published with Kole in *Biochemistry*, he stated "The possibility that the [RNase P] RNA molecule participates in the formation of an active site of an enzyme appears novel."[13] Direct experimental evidence for this heretical suggestion came two years later, when Sid's postdoctoral fellow Cecilia Guerrier-Takada assayed the effect of magnesium on the activity of reconstituted RNase P from *E. coli* and *B. subtilis*. In a supposed control reaction containing 60 mM magnesium, M1 RNA alone without protein specifically cleaved a precursor tRNA substrate with efficiency that approached that of intact RNase P![14] (Figure 3) The catalytically active moiety of RNase P under these conditions was not the protein, nor even the intact protein-RNA complex, but rather the RNA molecule itself. M1 RNA did not just participate in the formation of an active site; it was sufficient for enzymatic activity

and acted as a true enzyme. That is, it was not consumed or altered in the reaction, it functioned at sub-stoichiometric concentrations compared to substrate, and it catalyzed multiple rounds of cleavage of separate molecules. This epochal discovery was published in *Cell* in 1983 with the unambiguous title, *The RNA Moiety of Ribonuclease P is the Catalytic Subunit of the Enzyme*. Guerrier-Takada was the first author of this seminal paper and Norman Pace and members of his team, now collaborating with Sid, were co-authors.

These extraordinary results were initially met with disbelief. The M1 RNA used in the reaction had been subjected to SDS-phenol treatment and protease digestion, but was it truly devoid of protein? This objection had also been leveled at the in vitro RNase P reconstitution experiments, and it was similar to the argument used unsuccessfully forty years earlier to challenge Avery's monumental discovery that DNA carried genetic information. But Robin Reed, a graduate student in Sid's lab, cloned and sequenced the M1 gene from *E. coli,*[15] and Sid and Guerrier-Takada then synthesized M1 RNA by in vitro transcription of the cloned gene and showed in 1984 that the synthetic RNA produced in the absence of the C5 protein displayed cleavage activity.[16] This elegant experiment helped convince the skeptics. So, too, did reinforcements arriving from out west.

In 1982, the year before Sid and Guerrier-Takada showed that RNase P RNA acted as an enzyme, Thomas Cech at the University of Colorado discovered that particular RNA molecules from *Tetrahymena,* a unicellular protozoan, could undergo self-cleavage and ligation in the absence of protein. Cech was thus the first to show that "an RNA molecule has the intrinsic ability to break and form covalent bonds."[17] He also noted that these self-splicing RNAs were not true enzymes because they did not act on separate substrate molecules and underwent only a single round of reaction, and he named them ribozymes to distinguish them from true enzymes. The discovery that two different classes of RNA molecules possessed catalytic activity normalized the radical idea that RNAs could be enzymes. Later work in many laboratories showed that RNA could catalyze not only phosphodiester bond breakage and formation, but also a variety of other chemical reactions, including, ironically, peptide bond formation during protein synthesis at the ribosome.[18] Thus, the central chemical reaction of protein synthesis is carried out by RNA, with the ribosomal proteins demoted to a supporting role.

The discovery that RNA could catalyze biochemical reactions was a paradigm shift that fundamentally changed our understanding of biochemistry and, indeed, of biology. For these discoveries, Sid and Thomas Cech shared the 1989 Nobel Prize in Chemistry.

(Figure 4) Their work was hailed at the time as the "most important and outstanding discoveries in the biological sciences in the past 40 years,"[19] and the press release from the Royal Swedish Academy of Sciences, which awarded the prize, stated that "Many chapters in our textbooks have to be revised."[20] It was also noted that the existence of catalytic RNAs was likely to provide insight into the origin of life because it bolstered the idea of an "RNA world" in which biological catalysis could occur without first having to figure out how to synthesize proteins.

Figure 4: Left panel. News conference at Yale the day the 1989 Nobel Prize in Chemistry was announced. Cecelia Guerrier-Takada, who performed the key reaction, is sitting on Sid's right. Right panel. Sid relaxing in Stockholm in December, 1989, where he was awarded the Nobel Prize. (See V. Gopalan, Tribute to Sidney Altman. *RNA* 10.1261/rna.079397.122 (2022) for original credits.

In addition to the Nobel Prize, Sid was awarded the Rosenstiel Award from Brandeis University in 1988 and the Lomonosov Gold Medal from the Russian Academy of Science in 2016. He was elected a fellow of the American Academy of Arts and Sciences and a member of the American Philosophical Society and the National Academy of Sciences. Sid had several other important achievements. Most notably, he served for four years as dean of Yale College. In that role, reflecting his own broad interests, he helped redesign the curriculum to include distribution requirements so the scientists would get a healthy dose of the humanities and the humanists would be exposed to the sciences. He was also involved in the Judaic studies program at Yale and was a past president of the board of trustees of the Joseph Slifka Center for Jewish Life at Yale.

In the years after he discovered the enzymatic activity of RNA, Sid and his laboratory conducted important mechanistic, kinetic, and mutational experiments on RNase P and its substrates. These experiments revealed that much of the M1 RNA sequence was dispensable for cleavage activity and that base-pairing between two RNA molecules could generate structures that were substrates for cleavage by RNase P because they resembled tRNA precursor molecules.[21,22] (Figure 5) In fact, it was possible to convert almost any RNA into a novel RNase P substrate by providing the appropriate hybridization partner. Based on this insight, Sid and his trainees devised strategies to design or select

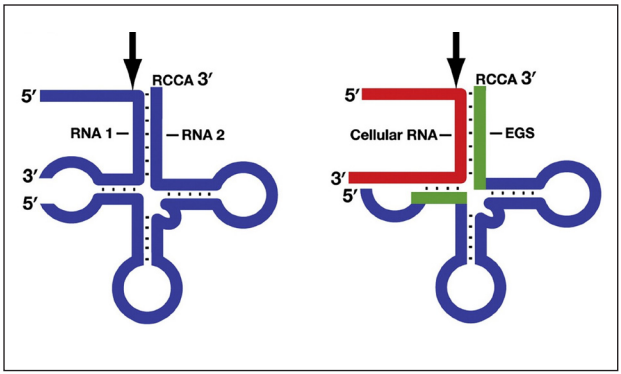

Figure 5: Left diagram. Reconstitution of an RNase P substrate by hybridization of two precursor tRNA-derived RNA molecules that base-pair to generate a structure that is then cleaved by RNase P. Cleavage site indicated by arrow. Right diagram. Base-pairing of an external guide sequence (EGS, in green) to a target mRNA (in red) generates a structure resembling a tRNA precursor that is cleaved by RNase P. Cleavage site indicated by arrow. (From W. H. McClain, L. B. Lai, V. Gopalan, Trials, travails and triumphs: an account of RNA catalysis in RNase P. *J Mol Biol* 397, 627-646 (2010).

short external guide RNAs that could be expressed or delivered in trans to base-pair with a target RNA and generate a molecule that could be cleaved by endogenous RNase P.[23,24] Alternatively, cells could be engineered to express M1 RNA fused to a short RNA segment that base-pairs with a target RNA, resulting in cleavage of the target.[25] These strategies resulted in the inactivation of specified viral, bacterial, and cellular RNAs, an approach with potential therapeutic applications.

Although it may be tempting to view the discovery of the enzymatic activity of M1 RNA as a singular event, an out-of-the-blue observation made in a control reaction, this view is inaccurate. Rather, the discovery was the culmination of work starting many years before the 1983 *Cell* paper and continuing after the paper was published. It began at the LMB around 1970 with Sid's discovery and sequencing of tRNA precursors and the detection of a processing activity in cell extracts, and it continued at Yale with the difficult purification of active RNase P, the detection of RNA in the pure enzyme, the discovery that the RNA subunit was required for enzymatic activity in vitro, the purification of inactive RNA and protein subunits and their reconstitution in vitro into an active enzyme, the demonstration that RNA was also required for RNase P activity in vivo, and the cloning and use of the M1 gene. As early as 1972, Sid made the novel suggestion that RNase P might be associated with a nucleic acid, and by 1981 he had the temerity to propose in print that RNA might directly contribute to enzymatic activity. The discovery that M1 RNA could act as an enzyme was not a lucky accident, but the result of a logical progression of focused and rigorous experiments conducted over many years.

Nevertheless, as always, luck did play a role. In an interesting evolutionary quirk, RNase P RNAs from Archaea and eukaryotes exhibit weak catalytic activity in vitro unless they associate with their protein subunits. Even for *E. coli* RNase P, M1 RNA in the absence of the C5 protein is inactive against some substrates, such as the 4.5S RNA precursor.[26] So, if Sid had switched to experiments in human cells or studied the "wrong" substrate, he would have missed his epochal discovery.

Sid encountered intense skepticism and criticism and even faced ridicule for his novel discoveries: the presence of RNA in RNase P, the RNA requirement for enzymatic activity, and finally the discovery that the RNA itself had enzymatic activity. During those difficult times, speaking invitations were rare, funding was hard to secure, manuscripts were frequently rejected out-of-hand, and professional relationships frayed and fractured. Sid's former mentor Matt Meselson encouraged him: "If you have done your experiments correctly…, then you have no choice but to trust what nature is telling you. Sooner or later, the truth will be apparent."[27] Meselson was right of course, but these indignities continued even after the validity of Sid's results was accepted and he was awarded the Nobel Prize. Twenty-five years after Sid discovered the enzymatic activity of M1 RNA, some commentators continued to minimize his scientific contributions. Then, Sid's longtime friend and LMB colleague Bill McClain, who had talked with Sid and Norman Pace at the time the key discoveries were made, gained access to the original laboratory notebooks and autoradiograms and discussed the experiments with some of the central participants. In 2010, McClain published a thoroughly researched account of the discovery of the enzymatic activity of M1 RNA, including a detailed timeline of the experiments.[28] This paper, published in the *Journal of Molecular Biology*, seems to have finally debunked the canard that Sid had received credit he did not deserve. Despite this final vindication, Sid was deeply wounded by the efforts to diminish his scientific legacy, and he never fully recovered.

Sid always told you exactly what he thought and was brutally honest. He was impatient with sloppy thinking and dismissive of experiments he deemed insufficiently rigorous. Thus, he often seemed brusque and acerbic. The first time we talked, when I was a student in one of his classes, he pointedly observed that students usually wanted to talk to him only to complain about a grade. But he also had a softer side. I called Sid the day his Nobel Prize was announced, and as we wrapped up the conversation he said, "But, Dan, we're still friends, aren't we?" He was amicable in social situations with friends and displayed his knowledge and interest in a wide range of topics. In a lengthy tribute to Sid published in the journal *RNA* after his death, numerous colleagues and former trainees

describe Sid's concern, warmth, and support at crucial moments in their lives and careers.[29] A retirement symposium in 2016 brought together many friends and colleagues, some of whom had known Sid since he was a graduate student, and the respect and affection for Sid were palpable. (Figure 6)

Figure 6: Speakers at a 2016 Symposium honoring Sid. Front row (left to right): Spyros Artavanis-Tsakonas, Matthew Meselson, Sidney Altman, Daniel DiMaio, and William McClain. Back row (left to right): Ling-Ling Chen, Ronald Breaker, Thomas Maniatis, Roger Kornberg, and Mark Ptashne. (Unpublished previously. Photo credit: Joseph Wolenski.)

In his later years as his health deteriorated, Sid would talk at length about science, current events, politics, his children, and his childhood. He proudly displayed a picture of his father's grocery store chock-a-block full of goods to sell. A favorite topic was baseball. He was a staunch (and frequently disappointed) Mets fan and on occasion attended games at Shea Stadium as a guest of the Wilpons, the team owners at the time. He was often spotted on and off campus wearing a blue and orange Mets jacket. In our final conversation, he told me one of his earliest memories. When he was a young child, he went with an uncle to see the Montreal Royals, the local minor league baseball team, and he was excited because he was going to see a Black baseball player for the first time, Jackie Robinson. But when he arrived at the ballpark, he was disappointed that Robinson wasn't in the lineup because he had been called up to the Brooklyn Dodgers to become the first Black major league player in the modern baseball era. Sid grudgingly admitted, almost seventy-five years later, that it was probably okay that he didn't get to see Robinson, considering the circumstances.

In 1972, Sid married Ann Körner, who was then a graduate student at Yale working with Dieter Söll. They raised two children, Daniel Altman and Leah Hazard. Daniel is an economist, author, and sports consultant living in New Jersey. Leah lives in Scotland and wrote a best-selling memoir, *Hard Pushed: A Midwife's Story,* that recounts her sometimes harrowing, sometimes humorous experiences as a practicing midwife. Sid's marriage ended in divorce in 2018. After a long illness, Sid passed away on April 5, 2022. At the time of Sid's death, he was the Sterling Professor Emeritus of Molecular, Cellular, and

Developmental Biology at Yale University, where he had been a faculty member for 50 years. In addition to Ann and his children, Sid is survived by four grandchildren.

Sid's extraordinary scientific contributions should also be considered in a larger context. He headed a small laboratory working independently or with a few collaborators to examine a phenomenon in bacteria that he found interesting even though there were no apparent practical implications. The work itself was hard-core biochemistry with rigorously designed experiments (and controls!). It did not depend on large consortia, genome-wide screens, nextGen and single-cell sequencing, the assembly of vast amounts of data that could be analyzed only with computers, or any of the other powerful methods ascendent in contemporary biological research. Rather, the problem was cracked at the bench by Sid and his trainees, who were driven by their passion to understand how life works. Small science. This approach may have particularly suited Sid's personality and his exacting standards, but it has fallen somewhat out of favor. How many other great discoveries are still lying in wait for the small laboratory? How many are overlooked by the juggernaut of big science?

ACKNOWLEDGMENTS

I first met Sid Altman in the fall of 1973, when I was a student in his course "Molecular Genetics of Prokaryotes." We became reacquainted ten years later when I joined the Yale faculty just before he published his seminal paper reporting the enzymatic activity of M1 RNA, and we remained friends until his passing. This memoir is based on my memories of Sid, the published record, a short biography of Sid written by his departmental colleague John Carlson and published in *Proceedings of the National Academy of Sciences,*[30] a series of tributes compiled by Sid's former fellow Venkat Gopalan and published in *RNA*, and Bill McClain's account of the discovery of the catalytic activity of RNase P RNA published in *Journal of Molecular Biology*. I thank Laura Nilson, Jonathan DiMaio, Miriam Schoenfeld DiMaio, Venkat Gopalan, and Tom Maniatis for critical review of drafts of this manuscript and for valuable suggestions. I also thank Nosha Vega for assistance in preparing this manuscript. I am particularly indebted to Tom Kelly for inviting me to write this article about a scientist I admired and respected for half a century.

REFERENCES

1. Altman, S., and L. S. Lerman. 1970. Effects of 9-aminoacridine on bacteriophage T4 deoxyribonucleic acid synthesis. *J. Mol. Biol.* 50:263–277.

2. Altman, S., and M. Meselson. 1970. A T4-induced endonuclease which attacks T4 DNA. *Proc. Natl. Acad. Sci. U.S.A.* 66:716–721.

3. Altman, S. 1971. Isolation of tyrosine tRNA precursor molecules. *Nat. New Biol.* 229:19–21.

4. Altman, S., and J. D. Smith. 1971. Tyrosine tRNA precursor molecule polynucleotide sequence. *Nat. New Biol.* 233:35–39.

5. Robertson, H. D., S. Altman, and J. D. Smith. 1972. Purification and properties of a specific *Escherichia coli* ribonuclease which cleaves a tyrosine transfer ribonucleic acid precursor. *J. Biol. Chem.* 247:5243–5251.

6. Stark, B. C., R. Kole, E. J. Bowman, and S. Altman. 1978. Ribonuclease P: An enzyme with an essential RNA component. *Proc. Natl. Acad. Sci. U.S.A.* 75:3717–3721.

7. Stark, B. C., R. Kole, E. J. Bowman, and S. Altman. 1978. See Ref. 6.

8. McClain, W. H., L. B. Lai, and V. Gopalan. 2010. Trials, travails and triumphs: An account of RNA catalysis in RNase P. *J. Mol. Biol.* 397:627–646.

9. Kole,R., and S. Altman. 1979. Reconstitution of RNase P activity from inactive RNA and protein. *Proc. Natl. Acad. Sci. U.S.A.* 76:3795–3799.

10. Gardiner, K., and N. R. Pace. 1980. RNase P of *Bacillus subtilis* has a RNA component. *J. Biol. Chem.* 255:7507–7509.

11. Kole, R., M. F. Baer, B. C. Stark, and S. Altman. 1980. *E. coli* RNAase P has a required RNA component *in vivo*. *Cell* 19:881–887.

12. Fraenkel-Conrat, H., and B. Singer. 1957. Virus reconstitution. II. Combination of protein and nucleic acid from different strains. *Biochim. Biophys. Acta* 24:540–548.

13. Kole, R., and S. Altman. 1981. Properties of purified ribonuclease P from *Escherichia coli*. *Biochemistry* 20:1902–1906.

14. Guerrier-Takada, C., K. Gardiner, T. Marsh, N. Pace, and S. Altman. 1983. The RNA moiety of ribonuclease P is the catalytic subunit of the enzyme. *Cell* 35:849–857.

15. Reed, R. E., M. F. Baer, C. Guerrier-Takada, H. Donis-Keller, and S. Altman. 1982. Nucleotide sequence of the gene encoding the RNA subunit (M1 RNA) of ribonuclease P from *Escherichia coli*. *Cell* 30:627–636.

16. Guerrier-Takada, C., and S. Altman. 1984. Catalytic activity of an RNA molecule prepared by transcription in vitro. *Science* 223:285–286.

17. Kruger, K, P. J. Grabowski, A. J. Zaug, J. Sands, D. E. Gottschling, and T. R. Cech. 1982. Self-splicing RNA: Autoexcision and autocyclization of the ribosomal RNA intervening sequence of Tetrahymena. *Cell* 31:147–57.

18. Nissen, P., J. Hansen, N. Ban, P. B. Moore, and T. A. Steitz. 2000. The structural basis of ribosome activity in peptide bond synthesis. *Science* 289:920–930.

19. Galston, A. W. 2002. Biology. In: *Science at Yale,* ed. S. Altman. New Haven, Conn.: Yale University Press.

20. Altman, S., and L. S. Lerman. 1970. See Ref. 1.

21. Guerrier-Takada, C., and S. Altman. 1986. M1 RNA with large terminal deletions retains its catalytic activity. *Cell* 45:177–183.

22. Forster, A. C., and S. Altman. 1990. External guide sequences for an RNA enzyme. *Science* 249:783–786.

23. Yuan, Y., and S. Altman. 1994. Selection of guide sequences that direct efficient cleavage of mRNA by human ribonuclease P. *Science* 263:1269–1273.

24. Plehn-Dujowich, D., and S. Altman. 1998. Effective inhibition of influenza virus production in cultured cells by external guide sequences and ribonuclease P. *Proc. Natl. Acad. Sci. U.S.A.* 95:7327–7332.

25. Liu, F., and S. Altman. 1995. Inhibition of viral gene expression by the catalytic RNA subunit of RNase P from *Escherichia coli*. *Genes Dev.* 9:471–480.

26. Guerrier-Takada, C., K. Gardiner, T. Marsh, N. Pace, and S. Altman. 1983. See Ref. 14.

27. Gopalan, V. Tribute to Sidney Altman. *RNA*, September 16, 2022; https://rnajournal.cshlp.org/content/early/2022/09/16/rna.079397.122.

28. McClain, W. H., L. B. Lai, and V. Gopalan. 2010. See Ref. 8.

29. Gopalan, V. 2022. See Ref. 27.

30. Carlson, J. R. 2022. Sidney Altman and the RNA revolution. *Proc. Natl. Acad. Sci. U. S. A.* 119:e2211692119.

SELECTED BIBLIOGRAPHY

1970 With L. Lerman. Effects of 9-aminoacridine on bacteriophage T4 deoxyribonucleic acid synthesis. *J. Mol. Biol.* 50:263-277.

With M. Meselson. A T4-induced endonuclease which attacks T4 DNA. *Proc. Natl. Acad. Sci. U.S.A.* 66:716-721.

1971 Isolation of tyrosine tRNA precursor molecules. *Nat. New Biol.* 229: 19-21.

With J. D. Smith. Tyrosine tRNA precursor molecule polynucleotide sequence. *Nat. New Biol.* 233:35-39.

1972 With H. D. Robertson and J. D. Smith. Purification and properties of a specific *Escherichia coli* ribonuclease which cleaves a tyrosine transfer ribonucleic acid precursor. *J. Biol. Chem.* 247:5243-5251.

1978 With B. C. Stark, R. Kole, and E. J. Bowman. Ribonuclease P: an enzyme with an essential RNA component. *Proc. Natl. Acad. Sci. U.S.A.* 75:3717-3721.

1979 With R. Kole. Reconstitution of RNase P activity from inactive RNA and protein. *Proc. Natl. Acad. Sci. U.S.A* 76:3795-3799.

1980 With R. Kole, M. F. Baer, and B. C. Stark. *E. coli* RNAase P has a required RNA component *in vivo*. *Cell* 19:881-887.

1981 With R. Kole. Properties of purified ribonuclease P from *Escherichia coli*. *Biochemistry* 20:1902-1906.

1982 With R. E. Reed, M. F. Baer, C. Guerrier-Takada, and H. Donis-Keller. Nucleotide sequence of the gene encoding the RNA subunit (M1 RNA) of ribonuclease P from *Escherichia coli. Cell* 30:627-636.

1983 With C. Guerrier-Takada, K. Gardiner, T. Marsh, and N. Pace. The RNA moiety of ribonuclease P is the catalytic subunit of the enzyme. *Cell* 35:849-857.

1984 With C. Guerrier-Takada. Catalytic activity of an RNA molecule prepared by transcription in vitro. *Science* 223:285-286.

1986 With C. Guerrier-Takada. M1 RNA with large terminal deletions retains its catalytic activity. *Cell* 45:177-183.

1990 With A. C. Forster. External guide sequences for an RNA enzyme. *Science* 249:783-786.

1994 With Y. Yuan. Selection of guide sequences that direct efficient cleavage of mRNA by human ribonuclease P. *Science* 263:1269-1273.

1995 With F. Liu. Inhibition of viral gene expression by the catalytic RNA subunit of RNase P from *Escherichia coli. Genes Dev.* 9:471-480.

1998 With D. Plehn-Dujowich. Effective inhibition of influenza virus production in cultured cells by external guide sequences and ribonuclease P. *Proc. Natl. Acad. Sci. U.S.A.* 95: 7327-7332.