THOMAS ARTHUR STEITZ

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Thomas A. Steitz was among the foremost of the generation that was responsible for an explosion in our understanding of the structure and function of biological macromolecules. His research career was one of sustained excellence over six decades, and spanned the range from determining the structures of important metabolic enzymes to understanding the structural basis of how genetic information residing in our DNA is used to make the proteins they encode. This latter effort culminated in the structure of the ribosome, for which he shared the Nobel Prize in Chemistry in 2009.

EARLY LIFE

Tom Steitz appears to have had an unremarkable but idyllic childhood growing up in the pastoral American heartland of the 1940s and ’50s. He did not come from a particularly privileged background, nor did he come from a long line of distinguished academics. At first glance, there was nothing in his early life that would predict he would go on to such a distinguished scientific career.

He was born on 23 August 1940 in downtown Milwaukee, Wisconsin, where his parents lived in an apartment above a paint store. His maternal grandfather and uncle were farmers (figure 1). Both of his parents had been to university: his father had a law degree from Marquette University in Milwaukee, and his mother had graduated from Carroll College, a small liberal arts college in Waukesha, now a suburb of Milwaukee. They valued education

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and expected their five children to do well in school (figure 2). Tom’s entire childhood was spent in downtown Milwaukee or its suburb of Wauwatosa, where he attended the local public (state) schools.

In high (secondary) school, in addition to academic subjects, Tom took courses in art, music and workshop training that covered electrical and metal work as well as woodworking. He built furniture and made an electric motor from scratch. Of this experience, he said: ‘I have found that the basic skills in working with tools and materials that I learned in the shop courses have proven invaluable for me in subsequent years, at home and in the laboratory including constructing models of proteins. I think it is unfortunate that such courses have been eliminated in many schools today as being unnecessary or too expensive’ (45)*. This comment is also relevant in Britain, where children typically narrow their range of study quite early, and academic students are often separated from vocational training such as the use of a workshop.

* Numbers in this form refer to the bibliography at the end of the text.
Tom wrote that he was not initially an excellent student, but started doing much better because he was spurred on when his younger brother entered high school. He noted that the girls in his class excelled in mathematics—only two or three of the top 10 were boys—and said, referring to a now infamous comment of Lawrence Summers: ‘I have never had any doubt that women are as good as or better than men in math, contrary to the impressions of a former president of Harvard.’ As was customary in those days, students were separated by ability, with the brightest students streamed into the most challenging courses, and Tom graduated eighth in his class of about 300 students.

Apart from his academic studies, Tom had some notable experiences. He spent many summer holidays working on his grandfather’s farm, working long days that lasted from 5 a.m. into late afternoon. He was paid for his labours, and used the money to buy himself a new saxophone, a bicycle and a tennis racket, in addition to saving money for college. Like many scientists, Tom enjoyed music and became proficient at the saxophone. He won awards at several contests and briefly considered music as a career, but concluded that he could do music as a hobby if he went into science, but could not do science as a hobby if he went into music.

While his childhood upbringing may superficially seem unremarkable, it was directly responsible for his blunt Midwestern manner, work ethic, meritocratic leanings and appreciation for building tools with his hands. As Heraclitus is alleged to have said, character
is fate, and these qualities served Tom well to take on some of the most difficult problems in structural biology.

UNDERGRADUATE EDUCATION

Upon finishing high school, Tom faced the choice of where to do his undergraduate studies. He was steered by a friend’s mother in the direction of Lawrence College (now Lawrence University), a small liberal arts college in Appleton, Wisconsin, less than a two-hour drive from his home. Lawrence College was known for its academic rigour, and, like top liberal arts colleges in America, required its students to study a broad range of subjects in addition to those related to their major. It was here that he learned to think critically, taking courses in a variety of humanities subjects including languages, philosophy, anthropology, history and religion. He ‘entered Lawrence with a heavy religious background and left it with an entirely different understanding of the origins of religious beliefs, their veracity, and their roles in cultures’ (45).

Liberal arts colleges are primarily undergraduate institutions that excel in teaching. Nevertheless, they have produced a large fraction of US Nobel Laureates, and contradict current thinking in the UK that teaching and cutting-edge research have to coexist in the same institution. However, they ensure that students are exposed to hands-on science through research projects, both within their campuses and by encouraging and arranging for students to do research in major universities during the summer. A chemistry professor of his, Bob Rosenberg, arranged for Tom to do a summer project at Northwestern University, where he studied the kinetics of catalysis by the proteases chymotrypsin, trypsin and thrombin, using various substrate analogues. Interestingly, Tom went on to do postdoctoral work on the structure of chymotrypsin.

In the summer before his final year of college, Tom attended a meeting on biophysics at Massachusetts Institute of Technology (MIT) for selected students from small colleges, which greatly influenced his career. His fellow students there included Mark Ptashne as well as Don Engelman, later to become Tom’s long-time colleague at Yale. It was there that he was inspired by lectures by Paul Doty on nucleic acids and Alex Rich on ribonucleic acid (RNA) and translation, both areas in which Tom would become famous later in life.

HARVARD AND CARBOXYPEPTIDASE A

It is not known where else Tom applied to graduate school, but he was certainly motivated to apply to Harvard by Paul Doty’s talk in the summer course the year before. He arrived there with the idea of working on the biophysics of nucleic acids, but American students normally do not begin their PhD research until the end of their first year. During the spring of 1963, around the time he had to choose a PhD adviser, Tom attended the three Dunham lectures by Max Perutz FRS. Using X-ray crystallography, the structure of myoglobin had just been solved to atomic resolution by Max’s former student and then colleague John Kendrew (FRS 1960), and they had won the Nobel Prize for their work the previous year. Max was a brilliant speaker, if also something of a showman. As Tom and others entered the auditorium, they were each given a pair of polaroid stereo glasses, and at some point Max
told the audience to put them on and asked the projectionist to show the first stereo slide, an occurrence that was as unusual then as it is today. As the three-dimensional (3D) image of over a thousand atoms in myoglobin materialized over Max’s head, there was a gasp from the audience (Moore 2018). Like most of the audience, Tom was stunned. He saw that this was the way forward to understand how biological molecules worked. Afterwards, Tom told a fellow graduate student, Peter Boer, that it was a pity nobody was doing protein crystallography at Harvard. On the contrary, Boer replied, Bill Lipscomb was working on a large enzyme using crystallography.

Lipscomb was already internationally renowned for his work on inorganic chemistry, notably the structure of boranes. He was originally from Kentucky and was jokingly referred to as ‘the Colonel’ after ‘Colonel’ Sanders, the founder of Kentucky Fried Chicken. Given his fearsome reputation, Tom approached him with some trepidation, perhaps exacerbated by the fact that he had already been turned down for PhD research by another faculty member (‘fortunately’, he said in hindsight). Luckily, Lipscomb accepted Tom without hesitation after the briefest and most informal of interviews, and thus began Tom’s long and illustrious career in X-ray crystallography.

As part of Lipscomb’s student training philosophy, Tom’s first project was to solve the structure of the small molecule methyl ethylene phosphate by direct methods (2). This gave him a solid foundation in crystallography and computing, and allowed him, during a rare absence of the Colonel, to come up with the novel idea of using direct methods (Sayre’s equation) to find the heavy atom positions from the heavy atom difference coefficients, leading to his first sole author publication (7).

At Harvard, Tom joined a superb group of postdoctoral fellows and graduate students, including Martha Ludwig, Hilary Muirhead, Flo Quiocho, Jean Hartsuck, George Reeke, J. C. Coppola and Paul Bethge, which led to the successful solution of the structure of carboxypeptidase (1, 3, 4, 6). Tom constructed a wire model representing the structure of carboxypeptidase, using the workshop skills he had learned in high school. Tom’s model is a historical signpost in the history of molecular visualization (3), showing how structures were represented before computer graphics (figure 3). Lipscomb, the Colonel, had a boyishly competitive streak, so when Tom departed from Harvard for Cambridge, taking the model with him, he had another one made and had it gold plated. Tom chuckled whenever he told this story of the two models.

As his PhD adviser, Lipscomb took more than a professional interest in Tom. Lipscomb was a keen clarinettist, and when he had been on the faculty at the University of Minnesota before he moved to Harvard, he played in a small chamber orchestra, where one of the flautists was a high-school girl named Joan Argetsinger (Joan Steitz ForMemRS 2014). On moving to Harvard, he was aware that Joan was a graduate student there with Jim Watson (ForMemRS 1981). In an inspired piece of matchmaking, he told Tom, who was a fine amateur saxophonist, that he should invite Joan to a chamber music session at his home. Clearly, the evening was a great success and Tom and Joan became a couple. Lipscomb was obviously pleased because he offered to go to Minneapolis and play at their wedding. Tom and Joan became one of molecular biology’s power couples. They were highly supportive of each other, which mattered a great deal in those days when women in science faced considerably more prejudice than today, and both went on to stellar careers in science.

Moore 2018
Aspartate transcarbamylase (ATCase)

Tom had wide-ranging interests and was always keen to pursue new and exciting directions. Towards the end of his PhD, following a lecture by John Gerhart from Berkeley—in which he described a new purification procedure for ATCase, a large allosteric enzyme with catalytic and regulatory subunits—Tom crystallized material supplied by Gerhart, and was the first author of the first paper from Lipscomb’s group on the structure of ATCase (5), a project initially taken over by Don Wiley and then worked on by many others in subsequent years. ATCase kept Lipscomb’s group occupied for over 40 years after Tom’s departure.
Figure 4. Protein Crystallography workshop in Hirschegg in 1968. Tom (centre) talking with Carl-Ivar Brändén (left) and Paul Sigler (right), with David Blow and David Davies in the background. Photograph courtesy of Jens Birktoft.

CAMBRIDGE 1967–1970 AND α-CHYMOTRYPSIN

Tom and Joan arrived at the Medical Research Council (MRC) Laboratory of Molecular Biology (LMB) in 1967 to start their postdoctoral work. Tom joined the group of David Blow (FRS 1972). Space was very limited in the MRC Lab in 1967. The Structural Studies Division had only three benches in total, one for David Blow’s chymotrypsin group, one for Max Perutz’s haemoglobin group and one for Aaron Klug’s (Aaron Klug, FRS 1969) virus group.

Soon after Tom arrived in Cambridge, there was a wonderful protein crystallography meeting in Hirschegg, Austria, organized by Max Perutz and Walter Hoppe. There were about 80 participants, consisting of virtually everyone involved with protein crystallography at the time. Figure 4 shows a photograph of Tom talking with Paul Sigler and Carl-Ivar Brändén, with David Blow and David Davies in the background.

Tom’s project in Cambridge was to find where substrates and inhibitors bound to α-chymotrypsin, with the goal of understanding the hydrolytic mechanism and specificity of its proteolytic enzyme activity, using data collected with an X-ray diffractometer. One of us (RH) had a similar goal, but using a Buerger precession camera for data collection. Consequently, Tom was able to calculate difference Fourier maps at low resolution (5 Å) in 3D, whereas Henderson could calculate only projection maps but at high resolution (2.8 Å). They worked independently for about a year in 1967–1968, consistently coming up with nothing or next to nothing. The difference Fourier maps were all blank or almost blank with occasional features
interpreted as artefacts. In the end, they decided to work together and make one last effort, collecting high-resolution data from crystals soaked in a high concentration of \(N\)-formyl-tryptophan, the smallest inhibitor that might bind in the restricted space available at the active site. It was basically a last throw of the dice: if that did not work, then the project would have to be abandoned. Tom hinted that, in the same way he had been helped by Martha Ludwig at Harvard when he had been a student, he was joining forces to help another young student with his PhD.

While they were agonizing over the problems, and having embarked on collecting data for the hoped-for formyl-tryptophan complex, Brian Matthews, who had dropped by on a visit, mentioned that he had used crystals containing 2% dioxan for collection of the native diffraction patterns three years earlier. Suddenly, it became clear that the reason that all the difference Fourier maps did not show any ligand bound to the active site might be that dioxan was occupying the hydrophobic binding pocket. Thus all the problems were solved, and within a few weeks the nearly hopeless situation was transformed into one where there was a multitude of highly informative maps showing how substrates and inhibitors bound. There was beautiful density for formyl-tryptophan, an excellent map showing bound dioxan and another map with \(N\)-formyl-phenylalanine. The paper describing substrate and inhibitor binding, helping to elucidate the mechanism of hydrolysis and explaining the specificity difference between trypsin and chymotrypsin, was soon published (9).

The work unambiguously identified the substrate binding site as a hydrophobic pocket with a serine at the bottom, but it posed a problem. Chymotrypsin cleaves at hydrophobic aromatic residues, while the homologous trypsin cleaves at basic residues. One might expect that, in the substrate binding site, there might be a change from a neutral to acidic residue between chymotrypsin and trypsin to indicate where the basic arginine or lysine would bind in trypsin, but a comparison between the published sequences of the two enzymes—for chymotrypsin by Brian Hartley (FRS 1971), and trypsin by Hans Neurath—showed no such change. Rather, at the bottom of the binding pocket where the indole ring of formyl-tryptophan was bound, the residue Ser-189 was replaced by asparagine in Neurath’s trypsin sequence.

In those days, all sequencing was done by tedious protein chemistry and it was notoriously difficult to distinguish between aspartic acid and asparagine. Normally, the decision was made based on the amount of ammonia detected after acid hydrolysis and amino acid analysis by chromatographic methods. They guessed that Neurath had made a mistake and that residue 189 in trypsin was really aspartic acid. Brian Hartley and Ross Jakes agreed to resequence that peptide from trypsin, and indeed a few weeks later confirmed its identity as Asp-189 in trypsin. The situation was thus totally transformed: a desperate state of ignorance had changed within a few short months to one in which substrate binding, ligand specificity of the whole serine protease family and even the hydrolytic mechanism was understood.

Jens Birktoft and colleagues, in parallel, had identified another asparagine to aspartate error in the published chymotrypsin sequence (Blow et al. 1969). Residue 102 in chymotrypsin was also aspartic acid and not asparagine, as Hartley had published. They had discovered the ‘charge-relay-system’ in the serine protease family, in which the catalytic triad Asp-102/His-57/Ser-195 hydrogen bond network created the general acid/general base environment for peptide bond cleavage. Thus, Tom’s three-year postdoctoral stay in Cambridge was highly successful, yielding insights into the mechanism of chymotrypsin’s enzymatic reaction.

Meanwhile, Joan, who had been formally sponsored by Francis Crick FRS and Sydney Brenner FRS, was told by Crick on her arrival that there was no space for her to carry
out experiments and she could spend her time doing ‘library research’. Luckily, her stay in Cambridge was rescued by Mark Bretscher (FRS 1985), who offered to share his bench with her. However, she had to decide on her own project. There was considerable interest in trying to understand how ribosomes initiate at the correct position on mRNA. The idea floating around the lab was to isolate ribosome-protected fragments and use Fred Sanger’s (Frederick Sanger FRS) new RNA sequencing technology to determine the sequences. Since Joan had worked with the RNA bacteriophage R17, she knew how to make radioactively labelled phage RNA. Her project had been considered by many postdoc peers (all male), but they considered it too risky to generate a job back in the States within two years (the expected postdoctoral stint at that time). Joan took it on because she had nothing to lose—as a woman she never expected to compete for a faculty position. She successfully determined the complete nucleotide sequences of all three ribosomal binding sites in the RNA where protein synthesis of the three R17 proteins is initiated (8) and immediately afterwards defined the gene order (10). In those days, women could not be fellows of Cambridge colleges, but in a clever move, Mark proposed her as a ‘member of the room’, which gave her many of the privileges of a fellow, such as dining rights at high table. Joan’s association with Caius College also benefitted Tom, who had no connection to any college, since he could then gain access to the tennis courts by signing in as ‘Dr Steitz’. Their stay in Cambridge was often punctuated by trips to Europe, including hiking in the Alps with Mark and other friends (figure 5).
**RETURN TO THE USA**

Like many postdoctoral visitors from the USA in those days, even before he had arrived in Cambridge Tom had already arranged a faculty position at Berkeley upon his return to the USA three years later. As the time for his return approached, in the era before email and the Web and even prior to unscheduled transatlantic telephone calls, most communication was by letter, written by hand on thin blue airmail paper. Tom discussed many things with the Berkeley leadership, among which was Joan’s future professional status, but his attempts to negotiate with the Berkeley hierarchy by airmail were frustrating.

Eventually, on their way to Berkeley, Tom and Joan gave talks at both Princeton and Yale, and at each place, they were both offered faculty jobs as a result. Their stay at Berkeley proved unusually brief. As Tom described it, ‘When I got to Berkeley, I put the four job offer letters on the desk of the Chair of Biochemistry when I went to visit him in his office. I asked if there was any possibility of a job for Joan at Berkeley. He looked at the letters and looked at me and said, “She’s a woman. Women do not run their own lab; they work in the lab of their husband.” We went to Yale.’ This attitude was despite Joan’s superb publication record and obvious talent. In contrast, Fred Richards at Yale, who had been tasked with the merger of biophysics and biochemistry into a new Department of Molecular Biophysics and Biochemistry, used his great personal and political skills to engineer an offer of two fully equal and independent faculty positions at Yale for Tom and Joan. Together with his hiring of others such as Don Engelman and Peter Moore, recruited at the same time, and his colleague Hal Wyckoff, Fred assembled a structural biology group at Yale (dubbed WERMS by Tom, figure 6), and sowed the seeds of what was to become a modern world famous and highly productive research centre.

Both Tom and Joan went on to build substantial and highly successful research groups (figure 7). Both became early principal investigators with lifelong support and funding from the highly competitive Howard Hughes Medical Institute, and both reached the pinnacle of academic research achievement. Joan has received just as many if not more prizes for her research and is also well known for providing encouragement and being a role model for women scientists.

**HEXOKINASE: FIRST PROTEIN STRUCTURE AT YALE**

Tom’s initial work at Yale was prompted by a seminal suggestion from Brian Hartley that came in the second year of Tom’s postdoctoral stint in Cambridge. Brian had asked Tom what research project he planned to pursue when he left the LMB and went to Berkeley, to the position Tom had arranged before he arrived in Cambridge. When Tom said he wanted to solve the structure of an aminoacyl tRNA synthetase, which represented the key step that linked nucleotide sequence to protein sequence through the genetic code, Brian said: ‘There, there, my boy. That is an interesting problem, but you must work on something you can actually do successfully. I suggest you study the structure of hexokinase.’

Tom joked that he had to go to the library to find out what hexokinase was, but did discover that it was Dan Koshland’s archetypical example of an enzyme that undergoes ‘induced fit’ in which substrate binding, in this case glucose, induces a change in enzyme structure from an inactive to an active conformation. Hexokinase catalyses the transfer of the terminal
phosphate group from adenosine triphosphate (ATP) to the six-hydroxyl group of glucose. Koshland argued that, if the enzyme was rigid, ATP would be constantly transferring the terminal phosphate to any water molecule that occupied the active site in the absence of glucose, draining away the cell’s energy. In any case, at the end of the second year of Tom’s postdoctoral fellowship, he switched his attention to working on hexokinase, which gave him a head start when he began his lab at Yale.

Indeed, Tom’s group, consisting initially of Wayne Anderson and Bob Fletterick, soon solved the hexokinase structure (11–14), with and without glucose, and found the largest conformational change in a single-subunit observed at that time, clearly establishing that Koshland’s induced fit hypothesis was correct. This was a major conceptual advance in enzyme mechanisms.

**THE CENTRAL DOGMA**

Tom noted in his Nobel biography (45) that the pictures of their hexokinase structures with and without glucose have been published in far more textbooks than any of his later works.
But given his exposure to Crick and Brenner during his postdoctoral years at the LMB, it was not surprising that he returned to an abiding interest that was to occupy the rest of his career.

In 1958, Francis Crick proposed a scheme for the flow of information in biology that he called the central dogma of molecular biology, an appropriate name since by then Crick had become something of a high priest of molecular biology (Crick 1958). He proposed that genetic information flowed from nucleic acid to make protein, but never in the reverse direction. With the subsequent discovery of mRNA, this was expanded to state that information flowed from DNA to RNA to protein, but not in the reverse direction. While conceptually simple, the process is enormously complex, involving the replication of DNA, the transcription of DNA into mRNA and the translation of mRNA into protein. Several Nobel prizes have been awarded for shedding light on one or other aspect of the central dogma. Indeed, one was for the unexpected finding that RNA could in fact be back-transcribed to DNA by the reverse transcriptase enzymes present in many RNA viruses (Baltimore 1970; Temin & Mizutani 1970).

Every step of the process is controlled by complex enzymes. Polymerases are required for the replication of DNA as well as its transcription into RNA; aminoacyl synthetases are required to charge each tRNA with the appropriate amino acid; and the ribosome is involved in selecting aminoacylated tRNAs cognate to the codon on mRNA to add the new amino acid to a growing protein chain. Tom had originally been interested in solving the structure of a synthetase bound to its tRNA but, following Brian Hartley’s advice, had worked on hexokinase to start his career. Now he was impatient to return to his original interest. This was an odyssey that would last almost three decades, and, as Moore has pointed out, was not
for the faint of heart (Moore 2018). Many of the projects would last over a decade, spanning multiple generations of postdocs and students.

CAP AND PROTEIN-DNA RECOGNITION

In the late 1970s almost nothing was known about how a protein would recognize a particular sequence of DNA. Accordingly, David McKay, a postdoctoral fellow of Tom’s, began work on the structure of a small regulatory protein that bound DNA, the catabolite gene activator (CAP). With the structure of just the protein in the absence of DNA, one could only guess at how it might recognize DNA, and here Tom’s guess was spectacularly wrong. Never one to mince his words, he trumpeted their guess in the very title of the paper: ‘Structure of catabolite gene activator protein at 2.9 Å resolution suggests binding to left-handed B-DNA’ (16).

It was not such an outlandish idea for its time. The structure of left-handed Z-DNA had just been solved by Rich, Wang and colleagues (Wang et al. 1979) and there was much talk of regulatory sequences of DNA adopting left-handed helical structures. Tom was not the kind of cautious scientist who was afraid to speculate what his data might mean, the kind that the physicist Pauli (Wolfgang Ernst Pauli, ForMemRS 1953) once described as ‘not even wrong’. Indeed, a scientist who never makes any mistakes is probably too timid and cautious; but what distinguishes great scientists is how they recover from their errors. The mistake, which at the time was not obvious, was that it is extremely difficult to predict binding modes even when the structure of both partners are known. To Tom’s credit, his lab took almost a decade to determine the structure of CAP bound to DNA, eventually done by a brilliant graduate student, Steve Schultz. The structure, a tour de force for its time, showed that the protein recognized an unusual form of DNA that is bent by 90 degrees (20).

DNA POLYMERASES

Around the same time that Tom’s lab was solving the structure of CAP, they had already begun work on the structure of DNA polymerases, the enzymes that replicate DNA and are essential for cell division and maintenance of the genome. To start with, he chose the simplest of this class of enzymes, DNA polymerase I, the discovery and characterization of which had resulted in the Nobel Prize to Arthur Kornberg (ForMemRS 1970) almost two decades earlier. It later turned out that this enzyme is mainly involved in DNA repair, and the polymerase that does most of the replication, DNA polymerase III, is much larger and more complex—and, ironically, was discovered by Kornberg’s son, Thomas. That too was solved in Tom’s lab many years later, but not before work on simpler polymerases had yielded a wealth of understanding on how enzymes duplicate DNA and RNA. Polymerases often contain not only a polymerase activity that adds nucleotides to a new strand using one of the old strands as a template, but also contain proofreading activities—usually exonucleases that allow them to chew back the newly synthesized strand when they sense a mistake has been made. Around 1980, Dave Ollis began work in Tom’s lab on the Klenow fragment, a large proteolytic fragment of DNA polymerase I that retains the polymerase activity as well as its 3′–5′ exonuclease activity, but not the 5′–3′ exonuclease
activity. The structure of the Klenow fragment in complex with a deoxynucleotide (17) was followed by a series of structures of the enzyme, culminating a decade later in its structure bound to DNA, solved by Lorena Beese (24). The work on the Klenow fragment established a paradigm for how small, single-subunit polymerases work in general.

Other DNA polymerases followed, including that of intact Thermus aquaticus DNA polymerase, important not only for its thermal stability but also for its then ubiquitous use in polymerase chain reactions (27); DNA polymerases that belong to a family distinct from DNA polymerase I or its Klenow fragment, such as DNA pol α (36); and finally, DNA polymerase III, which carries out most of the actual replication (42).

Polymerases do not work by themselves. In the cell, they are part of larger complexes, termed the replisome, and they have auxiliary factors that aid processivity (the ability to replicate large stretches without pauses or falling off) as well as speed. One such factor solved in Tom’s lab was the so-called sliding clamp that completely surrounds the DNA duplex (33).

Although the structure of the Klenow fragment from Tom’s lab was the first structural work on DNA polymerases, subsequent work did not come from his lab alone. Much important and beautiful structural work on replication was done in the laboratory of John Kuriyan’ (ForMemRS 2015) lab at Rockefeller and then Berkeley, often a collaboration with the biochemist Michael O’Donnell at Rockefeller. And after her postdoctoral work with Tom, Lorena Beese continued to carry out some elegant work on the mechanism of DNA polymerases in her own lab at Duke University. This is an example of Tom’s generosity and attitude towards his proteges. He did not consider that anyone ‘owned’ a scientific problem, and he encouraged them to work on whatever interested them, even if it meant they would be competing with him. The flip side was that if a problem interested him, he was not inhibited from working on it simply because his proteges were. It is striking that even towards the end of his career, and nearly 40 years after the work on the Klenow fragment was begun in his laboratory, Tom’s lab continued to do cutting-edge work on polymerases, shedding light on their mechanism by obtaining many snapshots of the enzymes in action.

OTHER DNA ENZYMES

Along with these studies on DNA polymerases, Tom also directed his attention to other enzymes involved in DNA replication, namely those involved in recombination, which underlies fundamental biological processes such as when two duplexes of DNA exchange genetic material or new segments of DNA are inserted into the genome.

Thus, Tom’s lab elucidated the structures of the protein RecA, an ATPase that binds to single-stranded DNA during homologous recombination, where strand exchange can happen between the two duplexes anywhere in the homologous region (22, 23), and the structure of γδ resolvase, which promotes strand exchange during site-specific recombination, which occurs at defined sites (26, 39).

REVERSE TRANSCRIPTASE AND RNA POLYMERASES

While working on DNA polymerases, Tom turned his attention to two other classes of polymerases. In the 1990s there was considerable interest in the structure of viral reverse transcriptases, which transcribe viral RNA into DNA, often followed by integration into the
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host genome. In particular, the reverse transcriptase from HIV was of great interest, because it was the target of a number of drugs against HIV at a time when the AIDS epidemic was raging. Tom’s lab initially solved the structure of the HIV-1 reverse transcriptase complexed with an inhibitor (21) and followed this up with studies on other inhibitors.

The other class was RNA polymerases, which transcribe DNA into RNA. As with the Klenow fragment, Tom’s philosophy was to study the simplest systems first, where the experiments were easier and the fundamental process the same. Accordingly, he chose to study the single-subunit RNA polymerase from the bacteriophage T7. David Jeruzalmi in Tom’s lab determined the structure of the enzyme (in a complex with the transcriptional inhibitor T7 lysozyme) (29). It differed substantially in detail from a structure that had been published five years earlier (Sousa et al. 1993), and the structure from Tom’s lab is now generally accepted as correct. As with DNA polymerase, this work was followed by a number of structures bound with substrate and in various stages of the process, obtaining snapshots of the enzyme during initiation (31) and while actively transcribing (32), as well as understanding how the enzyme changes from one form to the other (38).

A CATALYTIC MECHANISM FOR SPLICING

Tom’s interest in the mechanism of DNA and RNA polymerases and Joan’s interest in splicing (she is the person who discovered that it takes place in large complexes called spliceosomes) led them to collaborate to propose a general two-metal-ion mechanism for catalytic RNA splicing (25). The paper was a major landmark with nearly 1000 citations. While they informally influenced each other’s work and career throughout their lives, this was the first of only four papers they published together, the last, published in 2021, posthumously for Tom (46).

tRNA SYNTHETASES

Having begun work on various aspects of the central dogma, Tom returned to the original problem he wanted to work on after his postdoc at the LMB when he began a collaboration with Dieter Söll to work on aminoacyl tRNA synthetases.

Translation of genetic information into protein is a two-step process. First a tRNA is specifically recognized by its synthetase to add the appropriate amino acid. The aminoacyl tRNA is then complexed with a protein factor, the GTP-bound elongation factor Tu (EF-Tu), which delivers it to the ribosome. Then, in a second selection step, the ribosome accepts tRNAs that are cognate for (i.e. match) the codons on the gene. Having evolved along with the rest of the protein synthesis machinery, these aminoacyl synthetases are among the oldest of protein enzymes, and fall into two roughly equal classes known as class I and class II. The two classes share no sequence or structural homology and thus have evolved independently. At that time, the structure of an isolated tRNA synthetase solved by David Blow’s lab had been known for over a decade (Irwin et al. 1976), but the structure of the synthetase by itself provided no insights into why the enzyme was specific for its particular tRNA, and yielded only a limited understanding of how it was so accurate in choosing the appropriate amino acid.

As a result of their collaboration, Tom and Dieter’s lab reported the structure of glutaminyl tRNA synthetase complexed to its tRNA and ATP (18) and followed this up with a detailed analysis of how the synthetase recognized the anticodon loop (19). The structure of a class I synthetase gave us our first glimpse into this key first step in translation of the genetic code. It
was followed by the first structure of a class II synthetase by Stephen Cusack (FRS 2015) and his colleagues (Cusack et al. 1990). Cusack, as well as Dino Moras, went on to solve a large number of synthetase structures to understand the specificity and accuracy of both tRNA and amino acid selection by these enzymes.

**THE RIBOSOME**

In the last part of his career, while continuing to work on polymerases and other aspects of the central dogma, Tom turned to the problem that would bring him his greatest recognition, the ribosome. This is the macromolecular complex where the code on mRNA is read and the protein is synthesized. The process itself is enormously complicated and many of its details are still being deciphered. The ribosome has to initiate at the appropriate point on the mRNA, accept the correct aminoacyl tRNAs that match the code at each step, catalyse the addition of the new amino acid to a growing protein chain and move by a precise codon before starting the cycle of amino acid addition all over again. Finally, it has to terminate when a stop codon is encountered and be recycled for a new round of translation. Much of the basic biochemistry of the ribosome had been worked out in the two decades after its discovery in the late 1950s, but a detailed understanding of any of the steps involved was held back because of a lack of a structure of the ribosome.

And therein lay a problem: the ribosome itself was enormous in molecular terms. All ribosomes consist of two subunits, with the small subunit binding mRNA and ensuring the fidelity of recognition of the code by tRNA, and the large subunit responsible for catalysis of peptide bond formation. These subunits are designated 30S and 50S in bacteria and together make up the 70S ribosome (the S refers to their Svedberg sedimentation coefficient). In higher organisms, the subunits are considerably larger, with the 40S and 60S subunits making up the 80S ribosome. Ribosomes are enormous in molecular terms—a mammalian 80S ribosome has about half a million atoms.

The history of ribosome crystallography and how Tom entered it is a complicated story that one of us has tried to capture in a book (Ramakrishnan 2018). Initially, it was not even clear whether ribosomes were identical objects that could be crystallized. The first hints of this came from the observation of regular 2D crystalline arrays in various tissues such as chick embryos (Byers 1966) or lizard oocytes (Taddei 1972). The first 3D crystals of the 50S subunit from a moderately thermophilic bacterium, *Bacillus stearothermophilus*, were reported in 1980 by Ada Yonath (ForMemRS 2020) and Heinz-Günter Wittmann (Yonath et al. 1980). Some years later, crystals of both the 30S subunit and the entire 70S ribosome from a more extreme thermophile, *Thermus thermophilus*, were reported by a group in Pushchino, Russia, headed by Marina Garber (Trakhanov et al. 1987). Two further advances took place during the 1980s. All macromolecular crystals suffer from radiation damage that limits data collection; however, for ribosome crystals the problem was quite serious and limited the ability to collect any data at all. It was known that lowering the temperature of data collection would reduce radiation damage, and an attempt to make this a general method by Håkon Hope (Hope 1988) proved essential. The second advance was that, while the original crystals of ribosomal subunits and the intact ribosome diffracted to quite low resolution (typically ca 10 Å), Yonath and her colleagues continued to investigate several species before discovering that 50S ribosomal subunits from the archaeon *Haloarcula marismortui* could diffract to 3 Å resolution (von Böhlen et al. 1991). At this resolution, it should be possible
to fit the nucleotide and amino acid residues into an electron density map and thus deduce a molecular structure.

Nevertheless, by the mid 1990s, 15 years after the first crystals were reported, there was not even a low-resolution map of the ribosome by crystallography. By then, Yonath’s group was the only one working on the ribosome (her collaborator Wittmann had died in 1991) and two meetings in 1995 and 1996 provided little assurance of any real progress towards a structure. At a meeting in Victoria, Canada, in 1995, many were far more impressed by the single-particle reconstructions of the ribosome shown by Joachim Frank using electron cryomicroscopy (cryoEM) (Frank et al. 1995). It was then that several people in the audience decided to embark on their own efforts to solve the structure of the ribosome; among them was one of us (VR), Harry Noller and Peter Moore, who was a long-standing colleague and collaborator of Tom’s.

Tom had been interested in the ribosome for a long time. It was, after all, the final step in the central dogma and a logical extension of his work on DNA and RNA polymerases. In the early days of crystallography, it was considered a form of poaching to work on crystals that had been discovered by others. By the mid 1990s, this tradition was no longer universal. Moreover, 15 years was certainly enough time to give someone a chance to have a crack at the problem. Accordingly, Tom and Peter decided to see if they could use the crystals of the 50S subunit discovered by Yonath’s group to somehow break the impasse in determining its structure. In doing so, they were lucky in recruiting two outstanding postdoctoral fellows: first Nenad Ban, and then Poul Nissen (figure 8).
The first problem was to see whether they could obtain even low-resolution maps with recognizable features to show they were on the right track. They adopted a two-pronged approach. The first was to obtain initial phases by molecular replacement, using a low-resolution single-particle cryoEM reconstruction generated by Joachim Frank. This had first been tried successfully for an icosahedral virus structure (Jack et al. 1975), but it was not clear that it would work for a large asymmetric structure like the 50S subunit. The second was to see whether they could use large heavy atom clusters (in this case, a cluster containing 18 tungsten atoms) to directly phase the ribosome using isomorphous replacement. Such clusters at low resolution should scatter like a super-heavy atom and perhaps contain sufficient signal. In the end, both approaches worked, and the resulting map at 9 Å resolution clearly revealed the presence of right-handed RNA helices (28). The importance of this breakthrough was apparent to Tom and his colleagues, who described it as ‘an important beachhead for launching an attack on the structure of the ribosome at higher resolutions’ (28). Indeed, even to those of us who were working on various aspects of ribosome structure and believed it could be solved, the paper provided confidence that it was a solvable problem.

The next two years saw a frantic effort by several groups to solve the structure of the ribosome or its subunits. Partial structures of the subunits at intermediate resolution were published in 1999 in which individual proteins and some RNA elements could be placed in the maps (Clemons et al. 1999) (30), followed shortly afterwards by a structure of the entire ribosome at 7.8 Å resolution in which the tRNAs were clearly visible (Cate et al. 1999). Then, a year later, Tom, Peter and their colleagues published the entire atomic structure of the 50S subunit (34) a few weeks ahead of that of the complete structure of the 30S subunit (Wimberly et al. 2000).

The 50S structure from Tom’s lab was a real watershed in the ribosome field. Apart from anything else, it was by far the largest RNA structure solved, and yielded a wealth of data on RNA folds and motifs, as well as on protein–RNA interactions. Along with their paper on the structure, Tom’s group published a second paper in which they had bound an inhibitor to the peptidyl transferase centre, the catalytic site in the 50S where peptide bond formation occurs (35). It immediately became apparent that the site was surrounded entirely by RNA elements, which definitively settled a long-standing question of whether the ribosome was a ribozyme. Ever since ribosomes were discovered, they posed a mystery: if the ribosome makes proteins and itself consists of proteins and RNA, how did it originate? Francis Crick had suggested that perhaps early ribosomes consisted entirely of RNA, and ribosomal proteins came later in evolution to improve the efficiency of the ribosome (Crick 1968). At the time, there was no idea that RNA could carry out chemical catalysis, but the discovery of ribozymes by Cech and Altman (Kruger et al. 1982; Guerrier-Takada et al. 1983) changed thinking about the ribosome. Biochemical experiments by Noller suggested that the ribosome was indeed a ribozyme (Noller et al. 1992), but they were not definitive. With the 50S structure there was no further doubt, and it lent strong support to the RNA-world hypothesis in which life emerged from a primordial form in which RNA both stored genetic information and carried out catalysis, possibly with the help of non-coded peptides, before the genetic code residing in DNA and complex proteins emerged.

The second paper also led Tom’s group to suggest a mechanism for catalysis. They suggested that the ribosome allowed precise orientation of the substrates (the peptidyl tRNA that holds the growing protein chain and the aminoacyl tRNA that brings in the new amino
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acid). They also suggested that it stabilizes the transition state. These two aspects of the mechanism are very general principles of enzyme action and true of most enzymes. The idea that caught people’s attention was the hypothesis that a particular base, A2451, would have a protonated N3, leading to a charge relay network that catalysed peptide bond formation. In this, Tom may have been influenced by his postdoctoral work on chymotrypsin, which involves a similar charge relay network. It is possible that he thought of the ribosome, which forms a peptide bond, as the reverse of a protease like chymotrypsin, which breaks one. They were also influenced by experiments done by their colleague Scott Strobel, which suggested that this particular base had an unusually high pK_a and was likely to be protonated (Muth et al. 2000). Whatever the case, it is clear that in his enthusiasm, Tom overreached. Subsequent experiments showed that the base was not unusual in its pK_a, and there were strong reasons to question the mechanism. However, just as with Tom’s earlier mistake of suggesting CAP bound to left-handed DNA, Tom’s and Scott’s labs collaborated to do a beautiful series of experiments with customized substrate analogues that showed that an induced fit on substrate binding played a major role (40). The work showed that a base that protected the ester bond between tRNA and the peptide from nucleophilic attack moved out of the way upon aminoacyl tRNA binding to allow the α-amino group of the new amino acid to attack the ester bond initiating peptidyl transfer. Strobel himself went on to do highly sophisticated experiments using isotopes to show precisely how the protons moved during the reaction to catalyse peptidyl transfer.

A large fraction of known antibiotics bind to the ribosome, and many of them had been discovered decades earlier. They were shown by Noller and his colleagues to bind to distinct regions of ribosomal RNA (Moazed & Noller 1987), but exactly how was unclear. Along with other ribosome structure groups, Tom and his colleagues determined the structures of several antibiotics bound to the large subunit (37, 41, 44). A controversy about how several important antibiotics, including chloramphenicol and macrolides, bound to the ribosome was resolved unambiguously in Tom’s favour (43). Based on this work, Tom also helped to found a company, Rib-X Pharmaceuticals, to develop novel antibiotics that target the ribosome.

Membrane proteins

Tom was good friends with his colleague Don Engelman, whom he had first met at that undergraduate summer programme in MIT. The two of them, along with Fred Richards, shared many activities, including work-outs at their local gym. Don had a long-standing interest in membrane proteins, and they started collaborating to try to understand how membrane proteins are inserted into the lipid bilayer. This resulted in their proposal of the helical hairpin hypothesis, where two α-helices would form a hairpin prior to spontaneous insertion (15). Although the field subsequently focused on the role of the signal recognition particle and translocases such as Sec61 for insertion of proteins into membranes, there is a resurgence of interest in the helical hairpin hypothesis, possibly assisted by proteins that, unlike Sec61, do not function as channels. This is particularly relevant in the context of tail-anchored proteins, for which their C-terminus is inserted in the membrane, and for mitochondrially synthesized proteins.
RECOGNITION

The ribosome world was transformed as a result of Tom’s research, which paved the way for much subsequent work on the ribosome, including the structure of the entire ribosome at various stages of translation. Tom’s wide-ranging achievements describing the structural basis of key processes in molecular biology made him a strong candidate for major awards. Over the years, he was awarded the Rosenstiel Award in 2000, the Keio Prize in 2006 and the Gairdner Prize in 2007. In 2009, he was awarded the Nobel Prize in Chemistry along with Ada Yonath and one of us (VR) for his work on the structure and function of the ribosome. He was elected a Foreign Member of the Royal Society in 2011.

Without their prize-winning work, most Nobel laureates would not be particularly distinguished. Tom was one of those rare scientists who excelled throughout his career, and the work on the ribosome for which he was awarded the Nobel Prize was the icing on the cake. In fact, for his work on RNA polymerases, he could easily have been a contender for the prize on transcription that was awarded to Roger Kornberg. He was considered one of the greatest structural biologists of his generation, with an exceptional eye for important problems, and someone unafraid to persist for years in solving each one of them.

Social life

Tom and Joan’s son, Jon, was born in 1980. They lived just east of New Haven, in Branford, Connecticut, in a house they designed themselves overlooking an inlet of Long Island Sound. Jon went on to undergraduate studies in their Molecular Biophysics and Biochemistry Department at Yale, but clearly resisted any parental pressure he may have felt to become a scientist, since he chose to become a professional baseball player after graduation. Tom joked that Jon’s signing bonus on joining his team was roughly equivalent in monetary terms to a Nobel Prize. Jon later quit baseball, obtained a degree in law, and now works in San Francisco.

Tom was a fellow of Jonathan Edwards College during his entire time at Yale, appreciating the broader social base across different topics that he encountered there. His professional life and his interactions with the administrative hierarchy at Yale were greatly helped by Peggy Eatherton, who for nearly 35 years was what he described as his facilitator, memory chip and coordinator.

No biography of Tom would be complete without mentioning his inordinate fondness for wordplay and puns, often gleefully eliciting groans from his audience. It was he who coined the acronym WERMS (figure 6) for the structural biology group assembled at Yale by Fred Richards. Once when at the gym, on seeing exercise balls weighing 4, 6, 8 and 10 pounds, he remarked to Don Engelman, ‘Hmm, no oddballs here’. In noticing that a stem–loop of RNA at the bottom of the 30S ribosomal subunit called the spur had inserted itself into the tRNA binding site of a neighbouring molecule in the crystal lattice, he said: ‘Ah, a SPURious interaction!’

Later years and death

Almost until the end of his life, Tom continued to work on various aspects of the central dogma. His broad interests and tenacious pursuit of important questions guaranteed his strong
support from funding agencies and the attractiveness of his group to younger students and postdoctoral scientists. Following the Nobel Prize, he also found himself in even greater demand as a speaker, which resulted in him often overcommitting himself to the point of exhaustion. At a meeting for young scientists in Lindau, Germany, he found himself suddenly unwell with a blocked pancreatic duct and had to be rushed back home to New Haven. He was diagnosed soon afterwards with pancreatic cancer and, after struggling with it for a few months, died on 9 October 2018.

Tom’s life and career had spanned protein crystallography from its very early years to the structure of the ribosome and beyond. At each stage, he had been at the forefront, often contributing innovations to crystallographic methods. He was also an exemplary mentor. Many of his former postdocs and students are now faculty members at top institutions throughout the world, and leaders in their own right. Many of them continue to do leading work in the areas pioneered by Tom, such as polymerases and the ribosome, and in effect are carrying on his legacy. Several have been elected members of the National Academy of Sciences.

Tom leaves behind a large body of work on allosteric enzymes and the structural basis of the central dogma that has transformed our understanding of modern biology and forms an important part of virtually all textbooks of biochemistry.

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