It is with great sadness that we write about the death of our friend and mentor Christine (Chris) Guthrie, who passed away on July 1, 2022, following a long illness. Chris was a stellar scientist who made important contributions to the understanding of pre-mRNA splicing, was an influential member of the scientific community, and was an inspirational teacher and mentor. For both of us, our time in the Guthrie laboratory was formative and inspirational, and we deeply regret her loss. Chris is survived by her husband John Abelson.

Early Years

Chris was born in New York in 1945, the daughter of writer Irene Kampen. Kampen’s first book, Life Without George (1), was autobiographical, with tales of life as a divorced single mother, raising a teenage daughter in a small New England town. This book then formed the basis for the successful 1960s television series The Lucy Show. Chris spoke of the odd experience of seeing many aspects of her own life played out in the series, particularly in the character of Chris, the daughter of the eponymous Lucy. Chris was briefly married to Stephen Guthrie and retained the surname following their divorce and throughout her career, having first published under this name.

Chris attended the University of Michigan, graduating with a degree in zoology. Following a lecture in her senior year, she became fascinated by the idea of reconstituting ribosomes, which had recently been achieved. This led her to undertake doctoral research in the laboratory of Masayasu Nomura at the University of Wisconsin, Madison. When first approaching the Nomura laboratory, Chris was told that girls can’t lift heavy rotors or stand long shifts in the cold room, but can do genetics. This characterization stimulated her all the more to make her mark. The finding that the recently developed in vitro ribosome assembly pathway was strongly temperature-dependent inspired Chris to the insight that ribosomes with otherwise mild defects in their synthesis might be prone to stalling at low temperatures due to trapping in local energy minima. This led her to generate and screen cold-sensitive mutants of Escherichia coli, leading to the identification of the first conditional mutations that block ribosome synthesis. This discovery was influential in demonstrating that the in vitro reconstitution of ribosomes reflected a biological process, and presaged how Chris would use powerful genetic approaches throughout her career.

Chris moved to a postdoctoral position at the Max Planck Institute (MPI) in Germany, but found the environment uncomfortably competitive and resolved to leave science. Fortunately, she met Bill McClain, then a new Assistant Professor at Wisconsin, who provided Chris with an environment to work on the processing of transfer RNAs (tRNAs) during phage infection. Chris was then offered a position at the newly forming, and almost unknown, Department of Biophysics and Biochemistry at the University of California, San Francisco (UCSF). She arrived in the summer of 1973 as the seventh member of the department and the first woman professor. She was to remain the
sole female professor in this department for the next 13 years!

A Laboratory of Her Own

The initial focus of the newly formed Guthrie laboratory was tRNA maturation. An impressive series of papers through the mid-1970s documented their strong progress, first on Bacteriophage T4, a popular and tractable system at the time, and then switching to genetic analyses in budding yeast. This work gave valuable insights into the folding of newly synthesized tRNAs and the links to processing.

The process of establishing a laboratory of her own, as she put it, was not without difficulties. Chris spoke of her insecurity engendered by the sexist and overly critical atmosphere, both in the Nomura laboratory and at the MPI. These were compounded by a negative midterm review and the tragic death of her mentor at UCSF, Gordon Tomkins, leading to a period of depression. Her own difficulties with mental health and depression inspired Chris to establish a laboratory that would support and nurture all its members, emotionally as well as scientifically. She maintained this goal throughout her long career, to the lasting benefit of generations of graduate students and postdoctorates.

A Key Transition

After being granted tenure at UCSF in 1979, fresh scientific discoveries led Chris to make a major transition in her research: to study pre-mRNA splicing. The discovery of pre-mRNA splicing had raised exciting, but unanswered, questions about how introns could be recognized and spliced. Work by Joan Steitz proposed that the small nuclear RNAs (snRNAs) might play a critical role in recognizing at least the 5' splice site in introns. Chris had been introduced to “the awesome power of yeast genetics,” as she memorably phrased it, by taking the Yeast Genetics course at Cold Spring Harbor in 1978. So, when it was discovered that introns are also present in some yeast mRNA genes, Chris was convinced that this would be an ideal system to study the mechanisms of pre-mRNA splicing, crucially allowing genetic tests of the proposed base-pairing between snRNAs and the intronic signals.

This change of direction was initially viewed with some skepticism by the broader RNA processing community. There were no known snRNAs in yeast, and the yeast pre-mRNA introns that had been identified were rare and, at first sight, appeared substantially different from mammalian introns. Fortunately, Chris trusted in herself and led her group to identify numerous nuclear RNAs in yeast, including homologs of the critical snRNAs involved in pre-mRNA splicing. The yeast snRNAs generally differed substantially in size and abundance compared to those in humans, so establishing that they were functionally and structurally homologous was an important step in demonstrating that pre-mRNA splicing mechanisms were conserved. This greatly accelerated the establishment of budding yeast as a major model system for splicing.

Splicing Breakthroughs

Discoveries by Chris made numerous, fundamental contributions to our understanding of pre-mRNA splicing. The identification and characterization of the yeast splicing snRNAs allowed Chris to unambiguously demonstrate the key requirement for snRNA-mRNA base-pairing interactions in the mechanism of splicing. Similarly, she identified RNA-RNA interactions between different snRNAs that allowed the snRNAs to construct an RNA-based machine forming the core of the spliceosome. Particularly notable was the discovery of the Y-shaped structure formed between the U4 and U6, which became an icon in the splicing field, and the realization that following the release of U4, U6 went on to form crucial, base-paired interactions with both the 5' splice site in the pre-mRNA and the U2 snRNA. When recent cryoelectron microscopy work finally revealed the structure of the intact spliceosome, Chris was thrilled to see that these genetically identified RNA duplexes indeed lie at the heart of the splicing machinery.

The process of splicing involves two successive transestification reactions that do not, in principle, require an energy input. It was, therefore, a striking finding when ground-breaking genetics from the Guthrie laboratory revealed key roles for RNA-stimulated ATPases (RNA helicases). These were shown to reconfigure snRNA–snRNA and snRNA–intron interactions during transitions between the major steps in the splicing process. Subsequent work from the laboratory uncovered ATP-dependent mechanisms that maintain splicing fidelity, based on interaction timing, providing insights that are relevant to many other systems. In a successful approach that recalled her earlier work on ribosome assembly, a collection of cold-sensitive mutants identified novel splicing defects with the splendid name of “bad response to refrigeration” or brr alleles. Further exciting findings linked helicases to the process of mRNA export to the cytoplasm via loading and release of transport factors and revealed connections between splicing and the chromatin structure of intron-containing genes. Together, this body of work underpinned the research of numerous other groups and played a major role in driving forward the entire field of pre-mRNA splicing.

Recognition

The many scientific achievements of Chris Guthrie were recognized by notable indicators of esteem. These include election to the American Academy of Arts and Sciences (1991) and the National Academy of Sciences (1993), the Genetics Society Medal (1997), the Women in Cell Biology Senior Career Recognition Award (1998), the RNA Society Lifetime Achievement Award (2006), and the American Society for Biochemistry and Molecular Biology-Merck Award (2011).

Mentorship and Style

Chris was an incredible mentor and teacher. Together with her colleague Keith Yamamoto, she developed the outstanding “Biological Regulatory Mechanisms” core course of the UCSF PhD Tetrad program. Through 40 years of research leadership, she nurtured and inspired the careers of dozens of students and postdoctorates, many of whom
themselves became leaders in RNA biology. Chris also impacted the broader communities around her. She was a driving force behind the recruitment and hiring of young faculty at UCSF that made that department the success it is today, as well as being an icon and leader in the RNA community.

One of Chris's unique features as a mentor and a role model was her openness to discussing the difficulties she had experienced in her career: through sexism, insecurity, and the absence of a nurturing environment. In response, she created an environment where the difficulties of science were acknowledged. This allowed students to develop, and eventually thrive, knowing that Chris would always support them, even when she set a high bar for performance and intellectual commitment. Chris also knew how to have fun, and work in the Guthrie laboratory constantly combined science and enjoyment. Impressively, this environment extended beyond Chris's immediate group and the Guthrie laboratory routinely adopted researchers from other groups, allowing them to share the supportive milieu. Although Chris is no longer with us, her many alumni and colleagues will long cherish her memory, and almost all consider themselves proud members of the "Guthrie family."

1. I. Kampen, Life Without George (Doubleday, 1961).