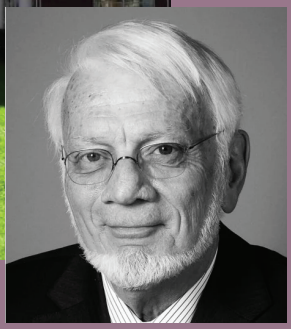
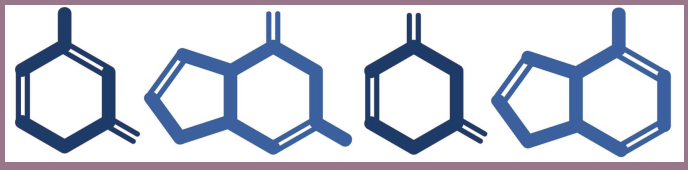
Tom and Joan Steitz RNA Fellows

Yale Center for RNA Science and Medicine





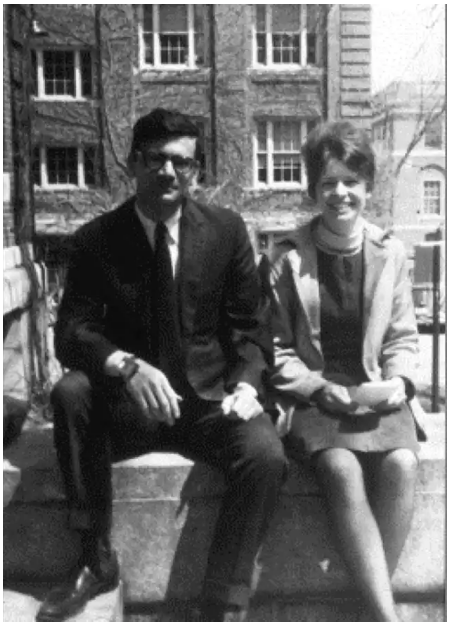
2023-2025

Background

Joan (left) and Tom Steitz (right)

Joan A. Steitz, PhD, Sterling Professor of Molecular Biophysics and Biochemistry and alumna investigator of the Howard Hughes Medical Institute, donated her 2021 Wolf Prize to the Yale Center for RNA Science and Medicine. Her contribution led to the founding of the Tom and Joan Steitz RNA Fellows Program, which will honor Yale undergraduate, graduate, and postdoctoral researchers who show promise as future leaders in the field of RNA biology. The goal of the fellowship is to create an intergenerational community of RNA scholars that will help foster the scientific excellence, career opportunities, and leadership potential of each awardee through alumni, peer, and faculty support. The program is inspired by Joan Steitz's extraordinary history of mentorship.

Award



Tom (left) and Joan Steitz (right)

Each class of fellows will be recognized in February at a special *Tom and Joan Steitz RNA Fellows Dinner*. The fellows' mentors will also be invited. The RNA Fellows from previous years will be invited back each year for the Fellows Dinner honoring the next class of Tom and Joan Steitz RNA Fellows, thus growing the community of fellows. In addition, the winning essays of each fellow in the new class will be published in the *Tom and Joan Steitz RNA Fellows Bulletin* disseminated annually to the community of fellows. The essays will also be publicly available on the Yale Center for RNA Science and Medicine website on the Fellows Program page.

The Yale Center for RNA Science and Medicine, which administers the Tom and Joan Steitz RNA Fellows Program, is led by director Karla M Neugebauer, PhD.

These are extremely exciting times in RNA science. Over the past few decades, researchers have discovered that RNA molecules are critical players in multiple areas of biology and biomedical science. Most recently, scientists have discovered that much of our genome, long believed to be silent, actually codes for RNA molecules. Although we are just beginning to realize how much remains to be understood about these RNAs and their functions, many of the new RNAs have already emerged as both critical diagnostics and key therapeutic targets in disease.

The mission of the Yale Center for RNA Science and Medicine is to build upon Yale's tremendous strengths in RNA biology, to foster interdisciplinary interactions and to apply our collective knowledge to understand disease processes and discover new treatments. Our members come from more than a dozen Yale departments and their laboratories are located at all three Yale campuses.

Center-sponsored events include our annual retreat, RNA Club, workshops, and seminars by leading researchers. Our goals are to foster a sense of community and to encourage collaborations, both between our world-class RNA scientists and with the many other extraordinary scientists and clinicians here at Yale.
If you should have any questions about the RNA Center’s mission, or have ideas for events you would like to see sponsored by the Center, please contact our leadership.

Tom and Joan Steitz RNA Fellows Class of 2023

Class of 2023 gathers for lunch:
Kyrillos Abdallah
Amer Balabaki
Kevin Chen
Sudheesh Parambil
Annsea Park—Medical Resident Stanford
Emily Sutton
Gaëlle Talross—Asst. Prof. University of Rochester

Tom and Joan Steitz RNA Fellows Class of 2024

Classes of 2023 and 2024 gather for lunch with Joan:
Zhiliang Bai
Hannah Barsouk—PhD Student Stanford Biochemistry
Moreen Ng
Leo Schärfen
Ethan Strayer
Lucille Tsao
Denethi Wijegunawardana
Ningning Zhang

Tom and Joan Steitz RNA Fellows Class of 2025

Michael Grome
Hannah Maul-Newby
Jessie Mohsen
Kyle Robik
Loren Wilson
Ling Xu

Michael Grome

Steitz Fellows Class of 2025
Postdoctoral Fellow,
Laboratory of Farren Isaacs

In nature, RNA serves as information, structure, and machine. RNAs function not only as recipes in protein translation but also as recipe decoders and chefs, cooking up the proteins essential for life. This versatility in the function and form of RNA, and nucleic acids in general, arises from the innate programmability of their chemistry. The central theme of my research has been leveraging the innate programmability of natural biomolecules, particularly nucleic acids, to engineer bottom-up and top-down artificial cell systems to address human needs.

In Chenxiang Lin's lab, I harnessed the programmability of DNA nucleotides to design and assemble DNA nanostructures that mimic the size, structure, and functions of natural membrane- remodeling protein complexes, inducing the tubulation of artificial lipid membranes. This work demonstrated the potential of nucleic acids to act as designable building materials for constructing functional, self-assembling, biomimetic machines with applications in programmable artificial cells, personalized drug delivery, and fundamental research.

In Farren Isaacs' lab, my focus shifted to translation where RNAs take on diverse roles in protein production. Here, RNA translates its four-subunit code into more chemically versatile 20-subunit proteins. While the standard genetic code consists of 64 codons redundantly encoding 20 amino acids and a stop function, deviations from this canonical code exist. These deviations occur when codons are reassigned to encode different amino acids or functions, producing alternative genetic codes. Such changes are enabled by variations in mRNA codon decoding by tRNA anticodons within rRNA-based protein synthesis machinery (ribosomes), which are further modulated by post-transcriptional modifications. My work focused on engineering alternative release factor and tRNA codon-recognition, redefining codon functions within bacterial translation. Doing so enabled us to rewrite and expand the genetic code, eliminating redundant synonymous codons and reassigning them to encode unnatural amino acids in synthetic proteins. This work established an artificial alternative genetic code while expanding the chemical capabilities of life.

As I transition into an assistant professor role, I aim to extend these genome-rewriting capabilities into more systems, ranging from microbes to plants. In these systems, mRNA secondary structure, transcriptional regulation, and tRNA decoding become increasingly cryptic and varied. My goal is to explore the unexplored biological mechanisms underlying noncanonical translation systems while creating genomically recoded organisms to manufacture biological tools and therapeutics unseen in nature, all within safe, sustainable biological settings.

Hannah Maul-Newby

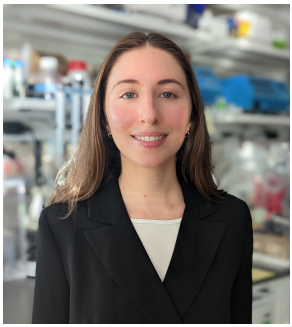
Steitz Fellows Class of 2025
Postdoctoral Fellow,
Laboratory of Stephanie Halene

Approximately 71% of Earth's surface is covered by water and only recently have scientists been able to explore the ocean's depths and begun to unlock her many unknowns. Like the ocean, RNA is diverse and profound; once regarded as the mere steppingstone between DNA and protein, RNA is recognized as a myriad of isoforms, gene transcripts and modifications that scientists are just beginning to unravel. I dedicated my PhD to dissecting previously unknown early spliceosomal assembly mechanisms in Dr. Melissa Jurica's lab at UC Santa Cruz. I studied the role of ATP in early spliceosome assembly and described a new role for DHX15, an RNA GTPase, in the disassembly of improperly formed complexes. My discovery of DHX15's new role highlighted the unknowns in splicing and mRNA processing and allowed me to contribute to our understanding of the complexities of the splicing macromolecular machinery. To build upon my interests in the mechanistic dissection of RNA processing and to apply my expertise to disease, I chose to pursue my postdoctoral work in Dr. Stephanie Halene's lab at Yale studying splicing factor mutations in hematological malignancies.

In Stephanie's lab, I study how splicing factor mutations commonly associated with myelodysplastic syndromes (MDS) and acute myeloid leukemia, impact RNA processing and contribute to disease progression. Thus far, these mutations have escaped successful therapeutic targeting due to their essential nature and the inability to target only the mutant versions of the proteins. To address this, I have begun to develop an interactome map across RNA processing utilizing complementary biochemical and molecular biology approaches including TRIBE STAMP and eCLIP and I have received DART-seq mice to dissect RNA modifications in primary murine MDS models. Mapping RNA modifications by eTAM-seq and direct RNA sequencing will provide unprecedented resolution of splicing effects on the epitranscriptome. Models of primary patient diseases will eventually allow me to develop and test novel therapeutic approaches.

Like exploration of the oceans' depths, unlocking the complex mysteries of RNA processing and their perturbations in disease, will require a strong commitment to studying RNA biology, creative thinking, fearless exploration, attention to detail, collaboration, and training trainees. I am committed to being that scientist and greatly look forward to expanding this work in the years to come as a postdoctoral fellow, Joan and Tom Steitz RNA Fellow and independent academic principal investigator.

Jessie Mohsen



Steitz Fellows Class of 2025
Graduate Student,
Laboratory of Sarah Slavoff

I came to Yale to study RNA, with so many experts in RNA science drawn to one place, I wanted to be here too. I burned my life down and built it up again just to get here. My introduction to bench work and research was a cross between nucleic acids and materials science. I had the great fortune to have Ned Seeman, the father of DNA nanotechnology, as my first scientific mentor. While he taught me so many life lessons (intentionally or not), one of the greatest gifts he instilled in me was a reverence for art. He sparked an entire field by drawing inspiration from M.C. Escher's Depth. He showed me all the ways we could control DNA and program it to form artwork on the nanoscale. While I dreamt of the DNA knots we were designing, I started to wonder about the artistry of the natural world. With three primary colors making an infinite array of shades, it is beautiful to wonder how the ancient world used four bases as the primary building blocks of life, and through permutations of these units, ancient life was made into art through elaborate and dynamic structures. The RNA world was made of millions of pieces of art, each possessing secrets that we as scientists devote ourselves to unveil, hoping to pull the curtain that reveals a sculpture on display. Each catalytic function, each motif, every hidden small open reading frame, depends on our scientific whimsy to uncover, inevitably leading to breakthroughs in basic science and medicine. RNA is the medium that my innate artistry is drawn to, and I see so many around me inspired by it as well. Louise Bourgeois told the world that "art is a guaranty of sanity" and as maddening as the pursuit of pushing the bounds of RNA science can be, its beauty must be what keeps us sane.

Louise Bourgeois

Kyle Robik

Steitz Fellows Class of 2025
Undergraduate Student,
Laboratory of Karla Neugebauer

As a high school student deeply curious about life, proteins and DNA seemed crucial. Then, after experiencing a world upended by an infectious RNA virus and lining up to get an mRNA vaccine, I became more interested in understanding DNA's sister. And, when my teacher twirled around a PDB structure to teach me about the numerous large ribosomal subunit proteins, I was instead struck by the sheer amount of RNA. Even the cellular protein machine relies on RNA: RNA can be a messenger, genome, and enzyme—RNA is the vital molecule for life!

In the summer of 2021, I joined the Neugebauer Lab to further explore my interest in RNA biology. Under the guidance of fabulous mentors, I worked on projects studying Downstream-of-Gene (DoG) transcripts and co-transcriptional RNA structure. These incredible experiences expanded my conceptions of the possibilities for RNA, and I eventually began working on my current project of elucidating a mechanism for all-or-none pre-mRNA processing.

During transcription, the nascent transcript undergoes processing events to produce a mature transcript. In the past decade, eukaryotic RNA processing and transcription have been shown to be coordinated. With the technology of nascent RNA long-read sequencing providing single-molecule Pol II position and splicing status, our lab discovered transcripts to be either spliced and cleaved ("all") or unspliced and readthrough ("none"). This so-called "all-or-none" pre-mRNA processing produces remarkable coordination between pre-mRNA splicing and 3'-end cleavage and is present across eukaryotes. My current research focuses on elucidating a mechanism for this phenomenon in budding yeast. U1 snRNP is known to bind to 5'SSs to initiate splicing; additionally, U1 was shown to suppress 3'-end cleavage when tethered near human poly(A) sites. I have tested the role of U1 snRNP in coordinating splicing and 3'-end cleavage with high-throughput nascent RNA long-read sequencing.

This work has only further deepened my passion for RNA biology. In particular, recent studies on U1 snRNP's physical interactions with Pol II and elongation factor activity have made me think about the possibilities for immense coordination in gene expression with U1 snRNP acting as a hub for transcription, splicing, and 3'-end cleavage. U1 snRNP is even composed of RNA! Forging a greater understanding of gene expression and its potential dysregulation in diseases excites me greatly. I plan to pursue a Ph.D. in Plant Biochemistry and continue exploring the unique role of RNA in plants, organisms crucial for agriculture and future climate change solutions.

Loren Wilson

Steitz Fellows Class of 2025
Graduate Student,
Laboratory of Sigrid Nachtergaele

The experience that inspired me to pursue RNA research was the final project of my undergraduate organic chemistry lab, where we were tasked with the synthesis of a compound of our choosing. Because of my nascent interest in biology, I chose to couple two amino acids via solution-phase peptide synthesis. It was truly humbling to spend weeks struggling to synthesize a single dipeptide, while ribosomes are able to orchestrate the assembly of long proteins with such speed and fidelity. I felt awe then, and the feeling has only grown stronger as I've learned about RNA's many forms and functions within the cell. What excites me most about RNA is its versatility. I love RNA because it can do it all: store information, catalyze reactions, and provide structure.

My current work in the Nachtergaele Lab revolves around RNA as a structural component. I use the paraspeckle, a nuclear body assembled on the scaffold lncRNA *NEAT1_2*, as a model to study the intersection of RNA modifications and nuclear body assembly, two areas of RNA biology that have thus far mostly been investigated separately. *NEAT1_2* localizes exclusively to the paraspeckle, providing a unique opportunity to study RNA modifications in a single subcellular location. My transcript-first, as opposed to modification-first, approach has led me to the discovery of the modification N^6-isopentenyl adenosine i^6A on *NEAT1*, the first reported case of this modification on a transcript other than tRNA. Loss of i^6A causes a reduction in paraspeckle number, which suggests that this modification does play a role in paraspeckle assembly. The function of the paraspeckle is still unclear, but a high paraspeckle count has been associated with cancer, viral infection, and neurodegenerative diseases, making them a potential therapeutic target.

When I think about the future, for RNA research and for biology in general, I often circle around to innovations of the past. PCR's origins in *Thermus aquaticus* and GFP's in *Aequorea victoria* make me wonder what other tools we may find in exceptional organisms, especially those with exceptional RNA. Recently, I have been excited by work in *Giardia*, which have a unique poly(A) signal, and in octopus, which have unusually high levels of RNA editing and high-fidelity ribosomes. Where else might we find regulation of RNA that diverges from conventional patterns? How might we learn from them?

Ling Xu

Steitz Fellows Class of 2025
Postdoctoral Fellow,
Laboratory of Anna Marie Pyle

The dynamic world of RNA, with its flexible structures and crucial roles in cellular processes, has captivated my scientific curiosity. I am particularly interested in contributing to our understanding of RNA structure and dynamics, especially in the context of RNA-protein/ligand interactions. Overcoming the challenges in visualizing these interactions is essential for developing RNA-targeting therapeutics, a promising frontier in medicine. By understanding RNA, we can strategically manipulate its function, leading to innovative therapies with broad implications for human health.

As a postdoctoral fellow in the Pyle lab, I am dedicated to unraveling the structural and dynamic complexities of introns involved in RNA splicing and retrotransposition. Leveraging my expertise in both structural biology and biochemistry, I have made significant progress in understanding these fundamental RNA processes. My cryo-EM structures of key intermediates in the group II intron splicing pathway have provided unprecedented molecular insights into the intricate conformational rearrangements that govern lariat formation and precise splice site selection. Our findings reveal that both group II introns and the modern spliceosome utilize similar mechanisms for splice site exchange, highlighting an evolutionary conservation of the catalytic core. Furthermore, I have successfully captured an intron RNP and its DNA-bound complex during retrotransposition, elucidating novel shape- and sequence-specific recognition strategies that guide the action of group II intron retrotransposon RNPs. This work offers valuable insights into the enzymatic mechanisms driving self-splicing introns, spliceosomes, and modern retroelements.

The significance of our intron research extends to potential therapeutic interventions. In fungi, the proper expression of certain housekeeping genes hinges on efficient intron splicing. By developing inhibitors that selectively disrupt this splicing process, we can effectively disrupt essential fungal respiratory pathway, presenting a novel strategy for antifungal drug development. In my recent project, I played a key role in elucidating the mechanism of a *de novo* inhibitor targeting a large, structured, self- splicing intron. The ability to target RNA with small molecules represents a paradigm shift in drug discovery, enabling us to target previously "undruggable" non-coding genes and challenging gene products. Our innovative pipeline, which efficiently integrates small molecule screening with high-resolution cryo-EM, yielded the first detailed *de novo* ligand- bound RNA structure, offering unprecedented insights into RNA-ligand recognition. My research underscores the transformative potential of RNA-targeted therapeutics to combat fungal pathogens and address a spectrum of human diseases, paving the way for innovative treatments for a range of diseases.

How to Apply

Eligibility

All current Yale undergraduate, Graduate and Post-doctoral Researchers are eligible.

Selection

An annual call for applications is made in January of each year. A committee of RNA Center Faculty members evaluates and selects awardees based on their personal essay, CV, and two letters of recommendation.

Please direct questions about the application to karla.neugebauer@yale.edu (not a member of the selection committee).

Yale Center for RNA Science and Medicine