Mary P. Edmonds

1922–2005

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Marlene Belfort

NATIONAL ACADEMY OF SCIENCES

MARY P. **EDMONDS**

May 7, 1922–April 16, 2005

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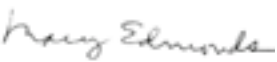

By Marlene Belfort

Mary Edmonds was a scientist before her time, someone who made profound contributions, from the early 1960s on, toward our understanding of messenger RNA (mRNA), the molecule that serves as a template for protein synthesis. Indeed, her group was among the first to provide convincing evidence of premRNA processing that generates the mature mRNA found in cytoplasm. Her contributions were in two primary areas: 3′-end processing and the chemistry of RNA splicing. Not only did she demonstrate that the end of the mRNA comprises a string of adenosine (A) residues to form a poly-A tail, but also she discovered the chemical nature of a branched nucleotide at what turned out to be the initiation site of mRNA splicing. These findings lie at the core of mRNA maturation.

After receiving her BA at Milwaukee-Downer College in 1943, her MA at Wellesley College in 1945, and her PhD at the University of Pennsylvania in 1951, Edmonds performed post-doctoral work at the University of Illinois from 1950 until 1952 and at the University of Wisconsin from 1952 until 1955. She then became a research associate at Montefiore Hospital in Pittsburgh from 1955 until 1965. Beginning in 1962, she occupied adjunct and research professor positions at the School of Public Health at the University of Pittsburgh, and in 1971 she finally achieved full faculty rank in the Department of Biochemistry, Faculty of Arts and Sciences, at the University of Pittsburgh. She moved to the Department of Biological Sciences in 1976 as a full professor, where she stayed until her death from complications of a heart attack on April 16, 2005.

Edmonds received several awards and honors during her career, including the USPHS Research Career Development Award, which supported her work from 1962 until 1971; the Doctor of Science (Honorary) from Lawrence University in 1983; and the President's

Distinguished Research Award from the University of Pittsburgh in 1989. She was elected to the National Academy of Sciences in 1991.

Defining the maturation of mRNA is what occupied Edmonds' research career. In 1960 she discovered a poly-A polymerase in thymus nuclei that required no DNA template (Edmonds and Abrams 1960). Soon after, she became aware of the natural occurrence of polyadenylate in calf thymus nuclei (Edmonds 1963). This was the likely product of the enzyme activity she had discovered three years earlier. She then isolated and characterized adenosine-rich polynucleotides in cellular RNAs (Edmonds and Caramela 1969) and in virion RNAs (Armstrong et al. 1972). The discovery of poly-A tails at the 3' ends of eukaryotic mRNAs (Edmonds et al. 1971) and the purification and characterization of the poly-A polymerase enzyme responsible (Winters and Edmonds 1973) were landmarks in the field. The discovery of poly-A sequences in bacterial mRNA soon followed (Nakazato et al. 1975).

(Photo courtesy Paula Grabowski, Department of Biological Sciences, University of Pittsburgh.)

The early 1970s was a ripe time for the discovery of poly-A mRNA, and along with the 1971 Edmonds paper in *PNAS*, two others were published in the same issue of the *Proceedings* by the Darnell and Brawerman Labs (Darnell et al. 1971; Lee et al. 1971). By isolating mRNA from polysomes, these three labs made the connection between the poly-A stretch and the mRNA. Thus, the 3' poly-A tract was added first to nuclear RNA (Edmonds and Abrams 1960) and then appeared in the polysomal translationally active mRNA (Jelinek et al. 1973; Nakazato et al. 1973). As noted by Darnell recently, poly-A "was the first strong suggestion of processing of large nuclear molecules in the formation of mRNA" (Darnell 2013). Said another way: These investigators were the parents of RNA processing.

The functional and practical importance of the poly-A tail in eukaryotic mRNA was soon recognized. The poly-A tail emerged as a binding site for molecular regulators of translation, RNA stability, and transport, as well as a hook for the isolation and purification of mRNA on polythymidylate cellulose (Venkatesan et al. 1976). This ability to readily isolate mRNA was transformative in efforts to define the molecule's structure and functions, and the polythymidylate cellulose purification strategy persists to this day in thousands of laboratories where researchers need to purify mRNA away from a background of more plentiful ribosomal RNAs. In this day and age, one would not consider doing a transcriptome analysis without first separating the mRNA based on its poly-A tail. One need only Google mRNA isolation, and literally dozens of companies that are marketing different kits for purifying the RNA based on its poly-A tail will pop up in the search results.

(Photo courtesy Paula Grabowski, Department of Biological Sciences, University of Pittsburgh.)

In the early 1980s, amidst the flurry of discoveries in the field of nuclear pre-mRNA splicing, Edmonds showed that poly-A RNA contains branched structures (Wallace and Edmonds 1983). She achieved this with chromatographic separation of complete nuclease digests of poly-A RNA, as well as the identification of nuclease-resistant tri-nucleotides, which contained 3' and 5' phosphodiester linkages to ribose. These refractory tri-nucleotides corresponded with the node of the intron lariat with a 2'-5' linkage to the branch-point adenosine. Although for us this is hindsight, Edmonds, in her 1983 *PNAS* paper titled "Polyadenylylated nuclear RNA contains branches," fully anticipated the importance of her result: "The occurrence of the branch in nuclear but not cytoplasmic polyadenylated RNA raises the possibility that it arises during the processing of hnRNA into mRNA…The possibility is suggested by its structural simi-

larity to a splicing intermediate that has been detected in wheat germ extracts" (Konarska et al. 1981).

The branched nucleotide was a profound discovery in RNA processing. In the words of Professor Magda Konarska, head of the Laboratory of Molecular Biology and Biochemistry at The Rockefeller University:

> *I first became aware of Mary Edmonds' work during my PhD. I was studying the mechanism of wheat germ RNA ligase that produces 2'-phosphomonoester, 3'5'-phosphodiester bonds, and naturally, I was intrigued by branched nucleotide structures that contained both 2'5' and 3'5' phosphodiester bonds that she detected in preparations of nuclear, but not cytoplasmic mRNAs. In fact, her work solidified my decision of selecting pre-mRNA splicing as a topic of my post-doctoral work, and that lead to a life-long fascination with this process.*

Once again, these fundamental insights had practical fallout, with a collaboration that resulted in the development of the antibodies specific to branched RNAs (Reilly et al. 1990). These profound discoveries in RNA processing, the poly-A tail, and the branched RNA led to Edmonds' election to the National Academy of Sciences in 1991.

Edmonds' persistence, integrity, and deep scientific insights resulted in an impressive career that withstood a decade of adjunct and research faculty status. She was generous and helpful to her colleagues as she went about her science in a modest, quiet, dedicated, penetrating, and unassuming way. Edmonds was a beautiful example of still waters running deep.

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