OBITUARY

Giuseppe Attardi 1923–2008

Douglas C Wallace

As the bombardment of the Allied advance descended on northern Italy in March of 1944, a young medical student was repeatedly forced to flee Padua. Yet Giuseppe Attardi persevered, receiving his MD from the University of Padua in 1947. Such was the dedication of this man who was purported to take his briefcase to the beach and who relentlessly pursued the molecular genetics of human mitochondrial DNA (mtDNA) in his Caltech sub-basement laboratory to within months of his death at 84.

In 1951, Attardi married Domenica Gandini-Attardi, with whom he shared a son, Luigi. In 1964, he married Barbara Furman, thus starting a personal and professional partnership that continued to 1975 and that contributed a daughter, Laura Attardi of Stanford's Radiation Oncology and Genetics departments, to the medical community. In 1982, Attardi married Anne Chomyn. This partnership continued to the end of his life and generated an array of important scientific advances in human mitochondrial biology and medicine.

Following completion of his medical studies, Attardi joined the Padua faculty as Assistant Professor of Histology and General Embryology, and he continued work there until 1957. During this period, he studied bacterial antibiotics and chick embryos and cells, publishing his first *Nature* paper, on animal vasculature, in 1955.

In the mid 1950s, Rita Levi-Montalcini, Attardi's life-long friend, suggested that he get further training in molecular biology. Accordingly, in 1957, he was awarded a Fulbright Fellowship to work in Melvin Cohn's laboratory in microbiology at Washington University in St. Louis. After two years with Cohn, he moved to the laboratory of Renato Dulbecco in the Division of Biology at Caltech, a mecca for budding young molecular biologists. There, with John Smith, he characterized ribosome-containing structures associated with virus replication, later recognized as polysomes.

Because of US visa restrictions, Attardi departed for France in 1961 as Chargé de Recherches in the laboratories of François Gros and François Jacob, Laboratoire d'Enzymologie of Centre National de la Recherche Scientifique (CNRS), Gif-sur-Yvette, and Pasteur Institute, Paris. During this period, studies on the regulation of lactose catabolism in *E. coli* were setting the stage for the enunciation of the Jacob-Monod operon model of coordinate bacterial gene regulation. Continuing his investigations of messenger RNA, Attardi published several papers in French and English with leading molecular geneticists, including Jacob, Walter Gilbert and James Watson.

In 1963, Attardi returned to Caltech as Assistant Professor in the Division of Biology and was promptly promoted to Associate Professor. By 1967, he had risen to Professor of Biology. During this period, he characterized nuclear ribosomal RNA transcripts and discovered heterogenous nuclear RNA, but then shifted his interest to mammalian mtDNA.

Attardi's transition to the study of HeLa cell mtDNA transcription was precipitated by two advances made at Caltech in the late 1960s: the purification of closed circular mtDNA from HeLa cells using cesium chloride–ethidium bromide gradients by Vinograd's laboratory and the analysis of DNA–RNA hybrids using the Kleinschmidt electron microscope technique by Norman Davidson's laboratory. By combining these two methods, Attardi and his colleagues were able to demonstrate that the mtDNA encoded a small and large rRNA as well as several tRNAs and to map their relative positions by 1976. The publication of the complete human mtDNA sequence in 1981 by the Sanger laboratory fully validated the Attardi map and permitted Attardi, Deanna Ojala, Julio Montoya and associates to establish the salient features of mtDNA transcription and RNA processing.

With the transcriptional map of human mtDNA resolved, Attardi, Chomyn and colleagues set out to define the function of the unidentified mtDNA polypeptide open reading frames discovered in the mtDNA sequence. This involved collaboration with Russell Doolittle's laboratory to synthesize peptides from the deduced mtDNA open reading frames, generation of peptide-specific antibodies, and precipitation and assay of the associated complexes. By 1986, they had concluded that the remaining seven unidentified reading frames were all subunits of respiratory complex I.

In 1970–1971, Attardi took a sabbatical as a Guggenheim Fellow in the laboratory of Boris Ephrussi, Centre de Génétique Moléculaire of CNRS, Gif-sur-Yvette. There, Barbara and Giuseppe Attardi discovered that in human–mouse somatic cell hybrids that segregate human chromosomes, the human mtDNA is selectively lost, whereas the mouse mtDNA is retained. Subsequent somatic cell genetic studies with colleagues including Andrew Wiseman and Michael King explored the cellular and genetic properties of mitochondria, culminating in the 1989 report using cells lacking mtDNA (ρ^o) as recipients in cytoplasmic hybrid (cybrid) transfers. This ρ^o technology permitted Attardi and several of his colleagues to demonstrate that pathogenic mtDNA tRNA and rRNA mutations caused discrete biochemical alterations, and to isolate and characterize a variety of mtDNA mutations in cultured mouse and human cells.

The correlation between mtDNA disease symptoms and aging phenotypes also prompted the Attardi laboratory to investigate the role of mtDNA mutations in aging. This led to Attardi's discovery with Yuichi Michikawa, Yan Wang and others that specific mtDNA control-region somatic mutations accumulate with age in particular tissues. The aforementioned trainees as well as many others continue Attardi's work in positions of authority and responsibility around the world.

For his seminal work on human mtDNA, Attardi was elected to the US National Academy of Sciences in 1984 and appointed to the Caltech Grace C. Steele Chair in Molecular Biology in 1985. He was subsequently recognized with many other awards, including the Feltrinelli International Prize for Medicine, the Gairdner Foundation International Prize and the Passano Foundation Award.

Giuseppe Attardi's career spanned a remarkable period for the biomedical sciences, extending from the elucidation of the structure of DNA to the characterization of the molecular basis of human disease. Although he was an important contributor to these extraordinary advances, he will long be remembered for his delineation of the structural and functional map of human mtDNA. ■

Douglas C. Wallace is at the Center for Molecular and Mitochondrial Medicine and Genetics, University of California, Irvine, California 92697, USA.
e-mail: dwallace@uci.edu