This Week's Citation Classic®

CC/NUMBER 16
APRIL 17, 1989

Borst P. Mitochondrial nucleic acids. *Annu. Rev. Biochem.* 41:333-76, 1972.
[Department of Medical Enzymology, Laboratory of Biochemistry, University of Amsterdam, The Netherlands]

This paper presented a fairly complete overview of the existing knowledge of mitochondrial nucleic acids, their structure, biosynthesis, function, and evolution. [The *SCI*® indicates that this paper has been cited in over 290 publications.]

A Treasure Trove for Molecular Biologists

Piet Borst
Netherlands Cancer Institute
Plesmanlaan 121
1066 CX Amsterdam
The Netherlands

February 13, 1989

I wrote most of this review in the summer of 1971 in the Department of Biochemistry of the University of Amsterdam. As I had underestimated the task, as usual, part of the writing was done during a vacation (with my wife and three small children) at the Lago Maggiore, Italy. I had been working on mitochondrial nucleic acids since 1964. This seemed a logical research topic after I had learnt mitochondrial basics as an MD-PhD student of E.C. Slater in Amsterdam and nucleic acid biochemistry in S. Ochoa's lab during a postdoctoral study of RNA phage replication in New York, together with C. Weissmann. By 1971 I had experience with DNA and RNA from a diverse set of mitochondria, and I had developed strong opinions about the field of mitochondrial biogenesis—hence, the strong stands in the review on controversial issues and the liberal inclusion of guesses where facts were scanty.

Some of these predictions survived. For instance, the prediction that resistance to antibiotics of mitochondrial protein synthesis would be due to alterations in mitochondrial ribosomal RNA rather than in ribosomal proteins was substantiated by later work. One issue is still not settled. I quote from the 1972 text:

> In conclusion then, there is no evidence that tumor mitochondria can be distinguished from normal mitochondria by any specific derangement in their genetic equipment. Since there is no evidence whatsoever for a derangement of mitochondrial function common to all malignant cells, it seems unlikely to me that further research on mtDNA of malignant cells will turn up a specific defect, although incidental defects may be found that could be useful in the elucidation of the genetic function of mtDNA and its replication.

In my opinion this still holds, but not everybody agrees.[1]

Why this inordinate number of citations? Primarily, of course, because the field grew explosively in the 1970s. Mitochondrial genes were identified and sequenced in a range of organisms, the unusual mitochondrial tRNAs and rRNAs were discovered, mitochondrial transcription was dissected, (optional) mitochondrial introns appeared on the scene with their maturases and self-splicing, and mtDNA sequence became a tool for studying evolution.

Even investigators who were emphatically not interested in mitochondrial nucleic acids found to their dismay that cDNA clone banks screened by differential hybridization often yield unwanted mitochondrial cDNAs. For these newcomers, who had no inclination to read all the old stuff, the 1972 review must have provided a convenient shortcut. It may have remained *en vogue* because nobody was foolish enough to attempt reviewing the entire field of mitochondrial nucleic acids again. Even recently it was quoted to justify sweeping generalizations about mitochondrial biogenesis, or historic detail about genes in mtDNA,[2,3] the closed circular character of animal mtDNAs,[4,5] or the fact that "all nuclear gene products involved in mitochondrial biogenesis are proteins,"[6] at least until the work of D.D. Chang and D.A. Clayton.[6]

My own work on mitochondrial nucleic acids continued through the 1970s, but petered out in the 1980s as I became engrossed in antigenic variation in trypanosomes, the glycosomes of kinetoplastida, and multidrug resistance in cancer cells. Former collaborators continued to work on mitochondrial nucleic acids in Amsterdam, however: Les Grivell on nuclear genes for mitochondrial proteins; Henk Tabak and Grivell on self-splicing of yeast mitochondrial transcripts; Tabak on mitochondrial RNA polymerase; Rob Benne and Paul Sloof on RNA editing in trypanosome mitochondria. Their results show that my defection from mitochondrial nucleic acids was premature and that the mitochondrial genetic system remains a treasure trove for molecular biologists.

1. **Shay J W & Werbin H.** Are mitochondrial DNA mutations involved in the carcinogenic process? *Mutat. Res.* 186:149-60, 1987.
2. **Tzagoloff A & Myers A M.** Genetics of mitochondrial biogenesis. *Annu. Rev. Biochem.* 55:249-85, 1986.
3. **Biswas T K & Getz G S.** Nucleotides flanking the promoter sequence influence the transcription of the yeast mitochondrial gene coding for ATPase subunit-9. *Proc. Nat. Acad. Sci. USA* 83:270-4, 1986.
4. **Tomkinson A E, Bonk R T & Linn S.** Mitochondrial endonuclease activities specific for apurinic apyrimidinic sites in DNA from mouse cells. *J. Biol. Chem.* 263:2532-7, 1988.
5. **Snyder M, Fraser A R, LaRoche J, Gartner-Kepkay K E & Zouros E.** Atypical mitochondrial DNA from the deep-sea scallop *Placopecten magellanicus*. *Proc. Nat. Acad. Sci. USA* 84:7595-9, 1987.
6. **Chang D D & Clayton D A.** A mammalian mitochondrial RNA processing activity contains nucleus-encoded RNA. *Science* 235:1178-84, 1987.

1A-16

CC/LS