This Week's Citation Classic

Szybalski E H & Szybalski W. A comprehensive molecular map of bacteriophage lambda. *Gene* 7:217-70, 1979.
[McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI]

A compilation of the physical and genetic mapping of a multitude of deletion and substitution mutants, together with available restriction maps and the sizes of many gene products, permitted construction of a comprehensive molecular map of the phage λ genome. This map serves as a reference source for all those working with phage λ, the well-developed model genetic system. [The *SCI*® indicates that this paper has been cited in over 260 publications.]

Elizabeth H. Szybalski
McArdle Laboratory
for Cancer Research
University of Wisconsin
Madison, WI 53706

April 25, 1987

In the late 1960s and the 1970s bacteriophage λ became one of the most important model systems in the field of molecular biology because of the wealth of information on its formal genetics, natural mechanisms for foreign gene cloning, integration, deletion formation, developmental pathways, transcriptional controls, and gene products. Aiding the molecular characterization of the λ genome was a new and ingenious method for physical gene mapping (formamide heteroduplex mapping), which was developed from 1967 to 1969 by Barbara Westmoreland through cooperation between the laboratories of Hans Ris and Waclaw Szybalski.[1] Because of my earlier interest in microscopy, I adopted this electron micrographic technique, which successively passed through our laboratory from Westmoreland[1] to Zdenka Hradečná to Michael Fiandt[2] and then to me.

The published physical λ DNA map represents the efforts of my colleagues together with about eight years of my intensive work in the dark basement of the electron microscopic laboratory of the McArdle Laboratory with many thousands of grids, negatives, and projection measurements. I first measured the lengths of single-stranded and double-stranded DNA molecule segments with a nylon fishing line pressed against a sticky projection board, but I subsequently adopted more sophisticated methods including the Numonic map reader. Each molecule had to be analyzed with frequent, intensive "detective work" to unravel the sometimes twisted or broken DNA strands. But it was fun!

Several approximate physical maps of λ DNA were published by W. Szybalski in various handbooks and manuals,[3,4] but we wanted to present the state of the art in this paper. We had already prepared a "final" map in 1974/1975 but since many new data were accumulating, we postponed its publication until 1979, when substantial nucleotide-sequencing data started to pour in. A finding that surprised me at that time was the oversaturation of the map indicating overlapping of genes.[5] Also, the map suggested to us important evolutionary implications.[6]

Although our formamide-based heteroduplex mapping technique was the most advanced tool for physical gene mapping in the late 1960s and early 1970s, restriction mapping and especially nucleotide sequencing have almost completely supplanted it. The most comprehensive sequence map of the λ genome (still partially based on our 1979 data) was published four years later;[7,8] *sic transit gloria mundi*!

1. **Westmoreland B C, Szybalski W & Ris H.** Mapping of deletions and substitutions in heteroduplex DNA molecules of bacteriophage lambda by electron microscopy. *Science* 163:1343-8, 1969. (Cited 365 times.)
2. **Fiandt M, Hradečná Z, Lozeron H A & Szybalski W.** Electron micrographic mapping of deletions, insertions, inversions, and homologies in the DNAs of coliphages lambda and phi80. (Hershey A D, ed.) *The bacteriophage lambda*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1971. p. 329-54. (Cited 230 times.)
3. **Szybalski W.** Genetic and molecular map of *Escherichia coli* bacteriophage lambda (λ). (Laskin A I & Lechevalier H A, eds.) *Handbook of microbiology*. Cleveland, OH: CRC Press, 1974. Vol. 4. p. 611-8.
4. ———. Genetic and molecular map of *Escherichia coli* bacteriophage lambda (λ). (Fasman G D, ed.) *Handbook of biochemistry and molecular biology*. Cleveland, OH: CRC Press, 1976. Vol. 2. p. 677-85.
5. **Szybalski E H & Szybalski W.** Physical mapping of the *att-N* region of coliphage lambda: apparent oversaturation of coding capacity in the *gam-ral* segment. *Biochimie* 56:1497-503, 1974. (Cited 65 times.)
6. **Szybalski W & Szybalski E H.** Visualization of the evolution of viral genomes. (Kurstak E & Maramorosch K, eds.) *Viruses, evolution and cancer*. New York: Academic Press, 1974. p. 563-82.
7. **Daniels D L, Schroeder J L, Szybalski W, Sanger F & Blattner F R.** A molecular map of coliphage lambda. (Hendrix R W, Roberts J W, Stahl F W & Weisberg R A, eds.) *Lambda II*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1983. p. 469-517. (Cited 50 times.)
8. **Daniels D L, Schroeder J L, Szybalski W, Sanger F, Coulson A R, Hong G-F, Hill D F, Peterson G B & Blattner F R.** Complete annotated lambda sequence. (Hendrix R W, Roberts J W, Stahl F W & Weisberg R A, eds.) *Lambda II*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1983. p. 519-676. (Cited 55 times.)

CC/LS