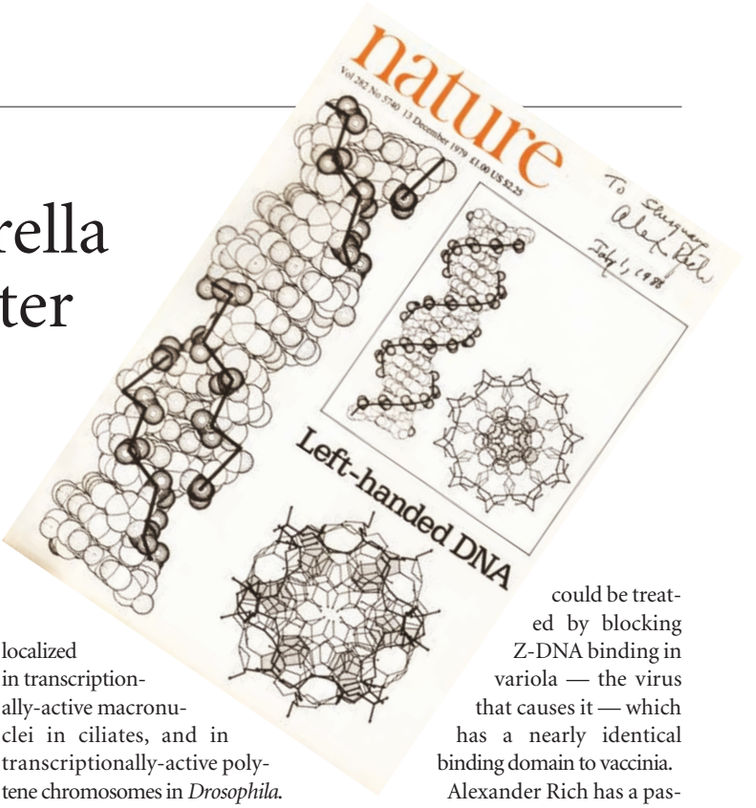
50TH ANNIVERSARY

More Cinderella than ugly sister

Watson and Crick changed biology forever when they described the right-handed double helical structure of DNA in 1953. Below, Shuguang Zhang gives a personal view on the less well-known story of the equally beautiful and functional left-handed DNA.



When I was an undergraduate in China, in 1979, I asked my biochemistry professor why all biological helices seemed to be right-handed, and whether there might be left-handed ones? My professor did not know. Shortly afterwards, my question was answered when Alexander Rich and colleagues reported the discovery of left-handed DNA.

Left-handed DNA consists of two anti-parallel chains, with bases that still form Watson–Crick base pairs. It was named Z-DNA as a result of its zigzag phosphodiester backbone. Before this unexpected discovery, DNA was viewed as structurally static. This finding made it obvious that the molecule is a dynamic entity: its structure depends on its environment.

The new discovery provoked a worldwide race to study Z-DNA. One key finding was that biologically negative supercoiling stabilized Z-DNA. This clearly indicated that Z-DNA could have a functional role.

To investigate this potential role, Rich's lab used antibodies to Z-DNA to probe nuclear activities. They found that the anti-Z-DNA antibodies localized in transcriptionally-active macronuclei in ciliates, and in transcriptionally-active polytene chromosomes in *Drosophila*.

Further studies by Rich's group, and others, were consistent with this finding, confirming that Z-DNA was involved in regulating some genes as well as chromatin remodelling. Studying unstable Z-DNA in cells is a technically daunting and unfashionable pursuit that has discouraged many. Undeterred, Rich and co-workers have pressed on alone, accumulating an impressive body of evidence that shows that Z-DNA is not only biologically relevant but is also important.

The latest exciting findings might indicate a link between the structure of Z-DNA and viral pathogenesis. In a series of experiments, Rich and colleagues show that the Z-DNA binding domain found in vaccinia viruses is required for them to be pathogenic. These results raise the intriguing possibility that smallpox could be treated by blocking Z-DNA binding in variola — the virus that causes it — which has a nearly identical binding domain to vaccinia.

Alexander Rich has a passion for Z-DNA and relentlessly pursues its biological function. His early passions led him to numerous discoveries, including the molecular structure of collagen with Francis Crick in 1955, DNA–RNA hybridization and the mechanism of protein synthesis on polyribosomes. I anticipate that Rich and colleagues will not only elucidate the biological function of Z-DNA, but will also inspire many more discoveries in the coming years.

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References and links

FURTHER READING
Wang, A. H.-J. *et al.* Molecular structure of a left-handed double helical DNA fragment at atomic resolution. *Nature* **282**, 680–686 (1979) | Kim, Y.-G. *et al.* Role for Z-DNA binding in vaccinia virus pathogenesis. *Proc. Natl Acad. Sci. USA* (in the press)

WEB SITE
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http://web.mit.edu/lms/www/index.shtml