## 9. Summary

This work reveals for the first time the structural basis for a protein, Zα, binding specifically to left-handed Z-DNA. The boundaries of Zα, an N-terminal domain of the dsRNA editing enzyme adenosine deaminase, ADAR1, were determined with limited proteolysis. Those experiments suggest that Zα is in fact part of a bipartite domain Zab. Nevertheless, the isolated Zα domain is capable of binding to Z-DNA with nanomolar apparent affinity. A complex of Zα together with a short 6-base pair DNA oligomer, d(TCGCGCG), including a dT overhang was crystallized. The structure was determined at 2.1 Å resolution using the isomorphous replacement technique, including anomalous scattering (SIRAS).

The structure shows that the bound DNA adopts an undistorted Z-DNA conformation, very similar to the Z-form in the pure DNA crystal structure determined by Wang *et al.* in 1979. Zα is a very compact domain consisting of a three-helix bundle closed on one side by a three-stranded antiparallel beta-sheet. The Zα-DNA contacts are made between residues from helix α3 and the C-terminal β-hairpin and mostly the zig-zag shaped phosphate backbone, characteristic of Z-DNA. One single base contact is observed to the exposed carbon 8 of a guanine base in the Z-DNA specific syn conformation. Unlike Z-DNA, in B-DNA all bases are in the anti conformation, not allowing for this interaction. Thus, in this tailored fit Zα recognizes the Z-DNA conformation through complementarity in shape and electrostatic nature. Surprisingly, Zα contains the helix-turn-helix (HTH) motif commonly found in B-DNA binding proteins. In Zα, this motif is used to contact Z-DNA in an entirely different mode from that seen with B-DNA. Together with recent experiments indicating that the HTH motif can also be used to bind RNA, this structure suggests that slight modifications in the HTH motif can result in dramatic differences in substrate specificity.