DNA double-strand break (DSB) repair pathways are essential for maintaining genome stability in cells. Non homologous end joining (NHEJ) is the major repair pathway employed by eukaryotes to mend DSBs produced during stationary phase. Many prokaryotes possess a minimalist NHEJ repair pathway mediated by two core proteins, Ku and ligase D (LigD), which together repair chromosomal DSBs. Mycobacterial LigD encodes a multifunctional NHEJ repair protein, comprising polymerase, nuclease and ligase domains.

The NHEJ polymerase (PolDom) possesses a wide variety of extension activities required for end-joining. We present the crystal structure of a pre-ternary complex PolDom bound to DNA. The complex contains a templated UTP bound in the active site, along with two manganese ions. A comparison of this structure with other polymerase complexes, suggests that is in a catalytically competent conformation, awaiting the arrival of an incoming 3′-OH (primer strand). We present further structural and biochemical data, which highlights the significance of this complex to NHEJ extension reactions and discuss the steps involved in concerted ordering of end binding, DNA synapsis and catalysis.