Data set	Zn peak	Fe peak	Mn peak
Wavelength (Å)	1.283	1.738	1.892
Space group	$P2_{1}2_{1}2_{1}$	$P2_{1}2_{1}2_{1}$	$P2_{1}2_{1}2_{1}$
Cell dimensions			
<i>a</i> , <i>b</i> , <i>c</i> (Å)	59.4, 82.8, 103.3	59.5, 82.8, 103.5	59.0, 82.8, 104.2
$\alpha, \beta, \gamma$ (°)	90, 90, 90	90, 90, 90	90, 90, 90
Resolution (Å) <sup>1</sup>	50-2.3 (2.43-2.3)	50-2.3 (2.43-2.3)	50-2.3 (2.43-2.3)
$R_{ m merge}$ (%)	3.7 (17.4)	4.7 (72.9)	5.6 (69.7)
CC <sub>1/2</sub>	0.999 (0.972)	0.998 (0.674)	0.998 (0.672)
I/σI	19.5 (4.9)	14.4 (1.5)	12.5 (1.4)
Completeness (%)	98.1 (96.6)	98.8 (96.9)	98.8 (96.8)
No. of reflections	43525 (6929)	43860 (6976)	44016 (6979)
Redundancy	3.5 (3.5)	3.4 (3.4)	3.3 (3.0)

## Supplementary Table 1. Summary of crystallographic information.

<sup>1</sup>The numbers in parentheses are for the highest resolution shell



**Supplementary Fig. 1. (A).** A titration with  $Mg^{2+}$  showing that it is not required for cleavage activity. **(B)**. A titration with  $Zn(OAc)_2$  showing that including zinc in the reaction buffer does not affect cleavage activity. **(C)**. A titration with FeSO<sub>4</sub> showing that including Fe(II) in the reaction buffer does not affect cleavage activity. **(D)**. A titration with FeCl<sub>3</sub> showing that including Fe(III) in the reaction buffer does not affect cleavage activity.



**Supplementary Fig. 2.** Titrations with decreasing concentrations of human mCF expressed in insect cells and human HCC expressed in human cells in the nuclease assays. The reactions were incubated for 1 h.



**Supplementary Fig. 3.** Plant glyoxalase II has a similar coordination network for metal ions in the active site as CPSF73. (A). The overall structure of *A. thaliana* mitochondrial glyoxalase II (PDB entry code 1XM8). The two metal ions in the active site are labeled. (B). Overlay of the binding mode of the two metal ions in the active site of CPSF73 (in color) and glyoxalase II (gray for protein residues). The bridging water/hydroxide is labeled W.