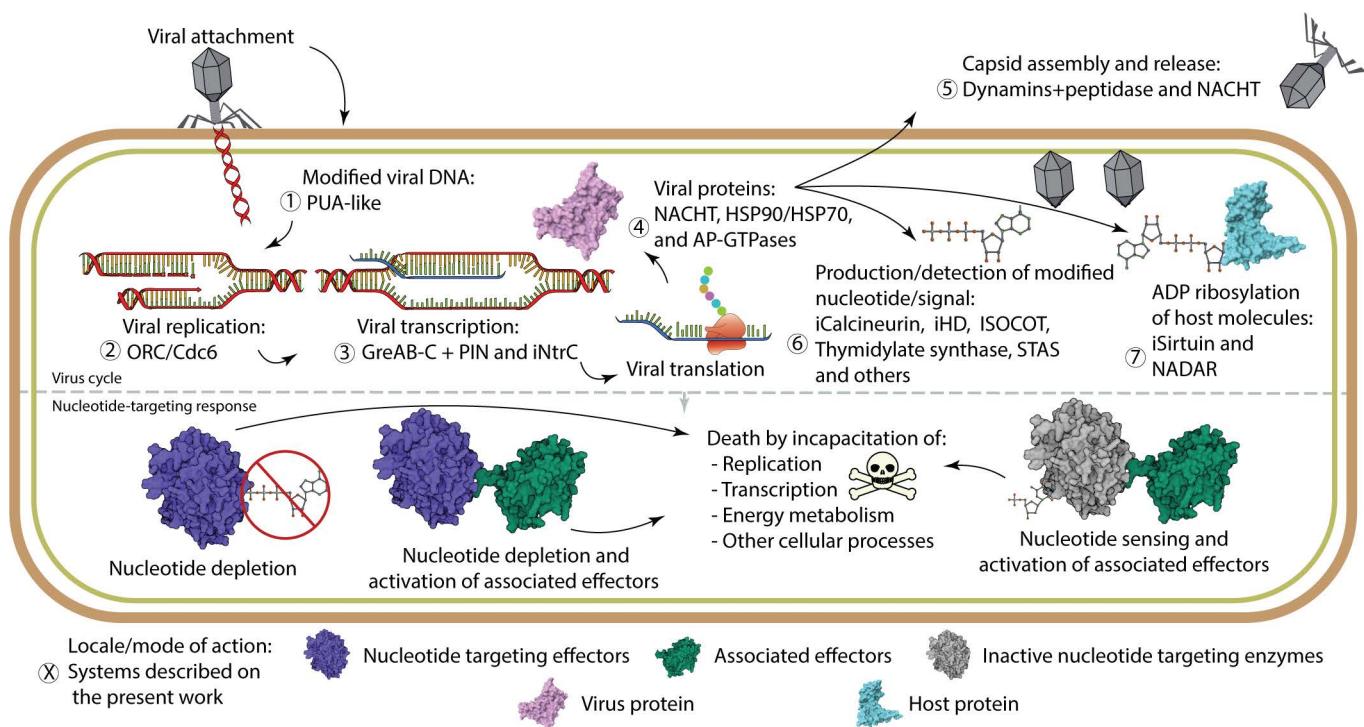


**Functionally comparable but evolutionarily distinct nucleotide-targeting effectors help identify conserved paradigms across diverse immune systems**

**SUPPLEMENTARY MATERIAL**

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## **TABLE OF CONTENTS**

- I.      Supplementary Figure Legends
- II.     Supplementary Figures
- III.    Supplementary Data
  - a.     Genome data
  - b.     Multiple sequence alignments
  - c.     Phylogenetic Tree

## I. Supplementary Figure Legends

**Supplementary Figure S1. Permuted GreAB-C structure model.** (A) Structure of the previously identified GreAB-C domain. (B) Alphafold model of a permuted GreAB-C domain. (C) Context of the permuted GreAB-C domain embedded in a sequence of divergent TPRs, forming a toroidal structure.

**Supplementary Figure S2. Double PIN structure model.** (A) Cartoon representation of the double PIN domain.  $\beta$ -strands are depicted in yellow,  $\alpha$ -helices in dark pink, and the HTH domain in dark cyan. Catalytic residues are shown in ball-and-stick representation.(B) Molecular surface representation demonstrating the occlusion of the active PIN site by the HTH domain. The two PIN domains are represented in purple, the HTH domain in green, and the position of the inactive catalytic residues of the inactive PIN domain is depicted in red.

**Supplementary Figure S3. Phylogenetic tree of the Orc/Cdc6 proteins.** The tree was constructed with IQtree2 using ultrafast bootstrap and SH-aLRT test as support values. The clades are labeled according to associated effector domains present in the genomic neighborhood.

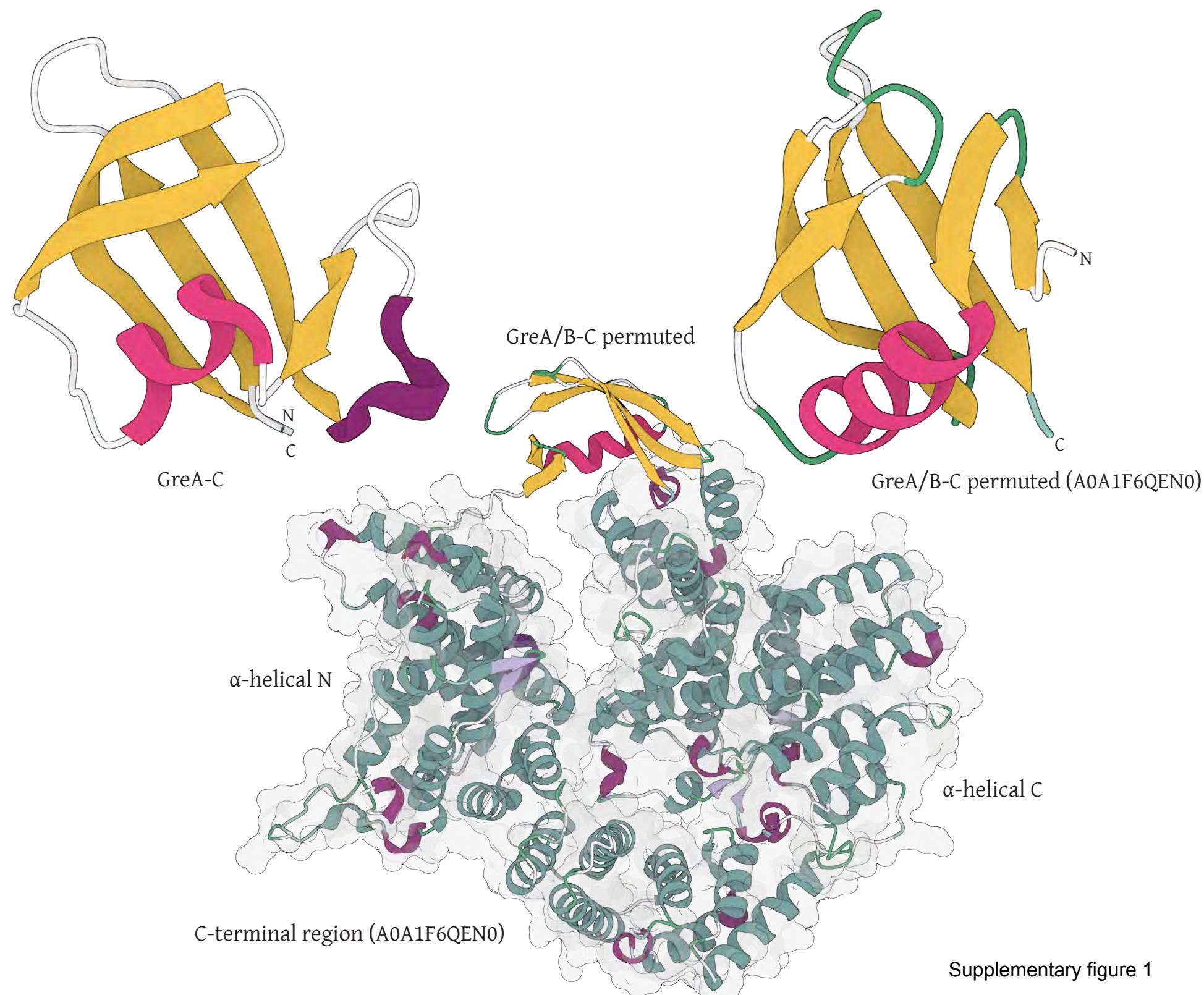
**Supplementary Figure S4. Sequence Logo of multiples Calcineurin families.** Sequences from various calcineurin homologues were gathered using previously characterized calcineurin PDB sequences as seeds. These sequences were aligned using the mafft local pair algorithm, and the logos representing different families were visualized using the Jalview software. Conserved motifs I-V are depicted and with boxes.

**Supplementary Figure S5. Activity site and conserved residues from the Calcineurin-CE domain.** (A) Alphafold modeling of the Calcineurin-CE domain (WP\_080633877.1). The residues conserved in the activity sites are shown in ball and stick representations. The synapomorphic asparagine is colored in orange. Sequence logo of the conserved regions are shown and the dotted lines indicate the start and end position of the logo in the structural model. (B and C ). Activity site of the experimental crystallized Calcineurin domain from the PDB 2NXF without and with the Zn<sup>+2</sup> ion respectively.

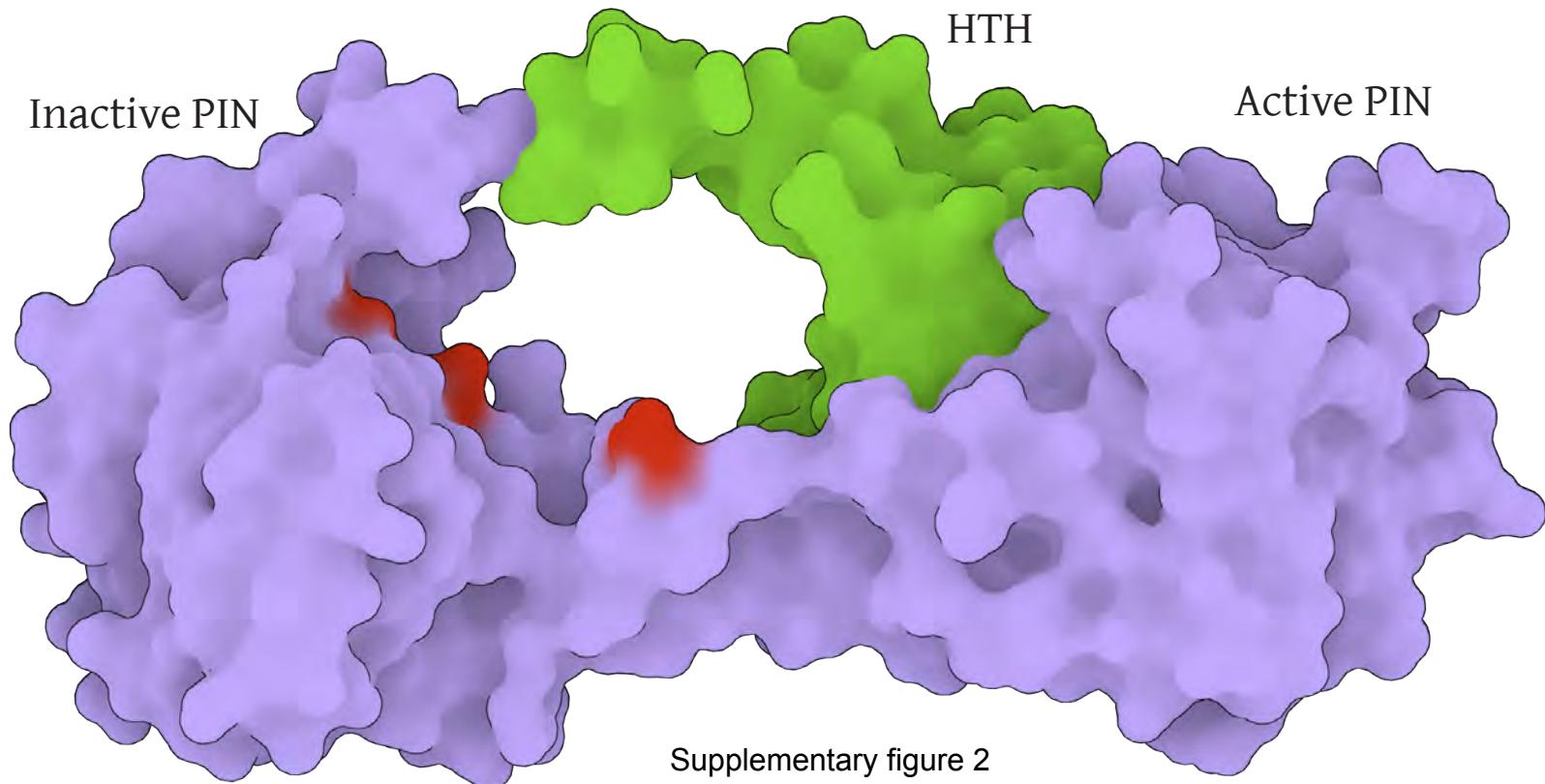
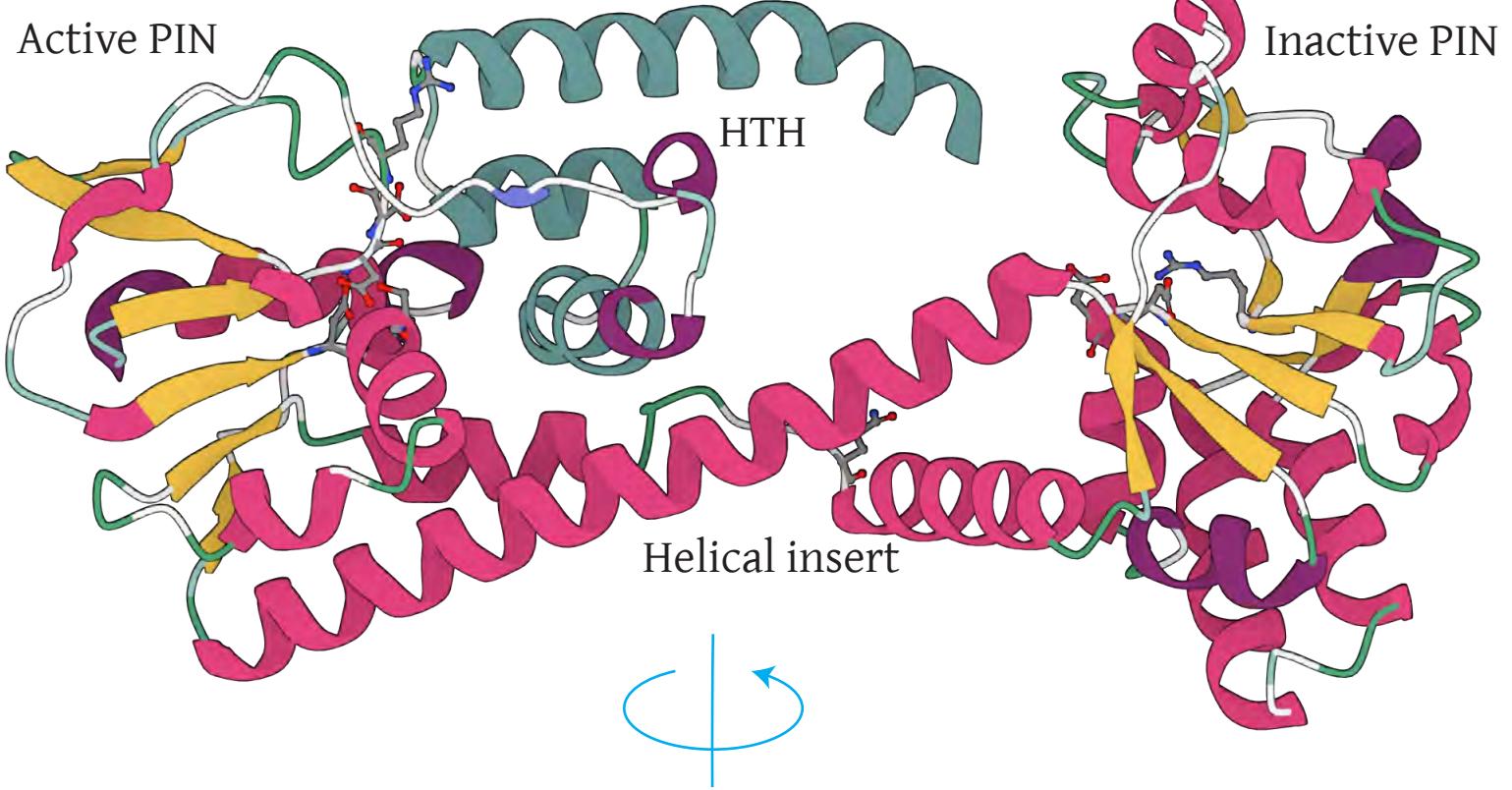
**Supplementary Figure S6. Activity site and conserved residues from the HD-CE domain.** (A) Alphafold modeling of the HD-CE domain (CZQ95560.1). The residues conserved in the activity sites are shown in ball and stick representations. The synapomorphic residues are colored in yellow. Sequence logo of the conserved regions are shown and the dotted lines indicate the start and end position of the logo in the structural model. (B and C ). Activity site of the experimental crystallized HD domain from the PDB 3G3N without and with the Zn<sup>+2</sup> and MG<sup>+2</sup> ions respectively.

**Supplementary Figure S7. Activity site and conserved residues from the PRTase-CE domain.** (A) Alphafold modeling of the PRTase-CE domain (NPV02125.1). The residues conserved in the activity sites are shown in ball and stick representations. Sequence logo of the conserved regions are shown and the dotted lines indicate the start and end position of the logo in the structural model. (B and C ). Activity site of the experimental crystallized PRTase domain from the PDB 5KNQ without and with the Mg<sup>+2</sup> ion respectively.

**Supplementary Figure S8. AlphaFold confidence score for the models produced on the present work .** On the left the structural models colored by the pLDDT scores. On the right the structural models as colored in the figures presented on the main text. Dark blue, light blue, yellow and orange represent a very high, confident, low and very low prediction respectively.

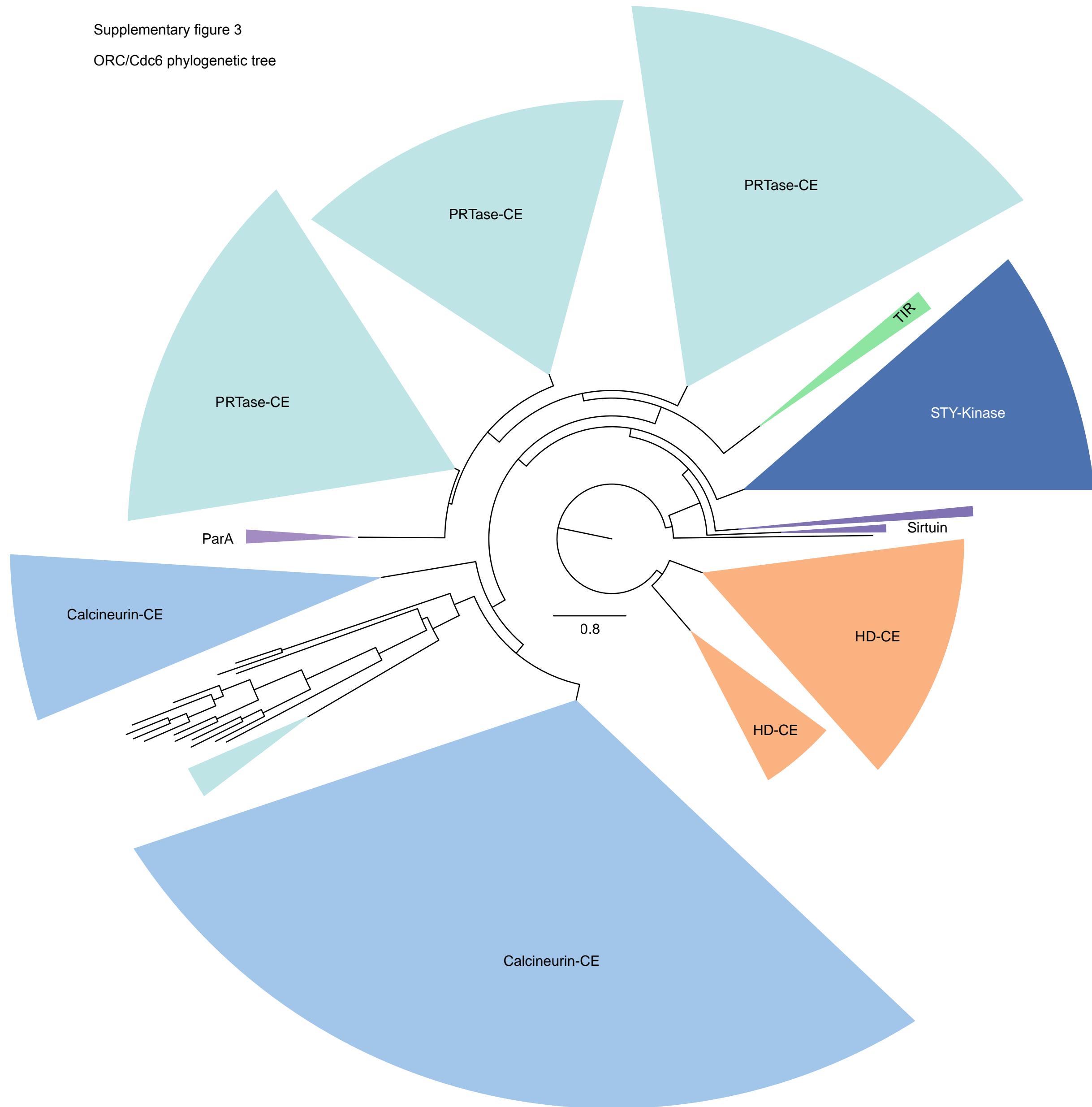


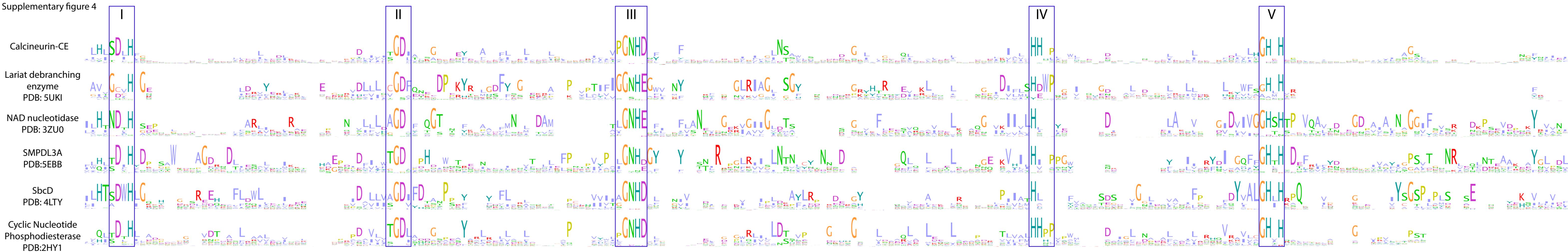
Supplementary figure 1



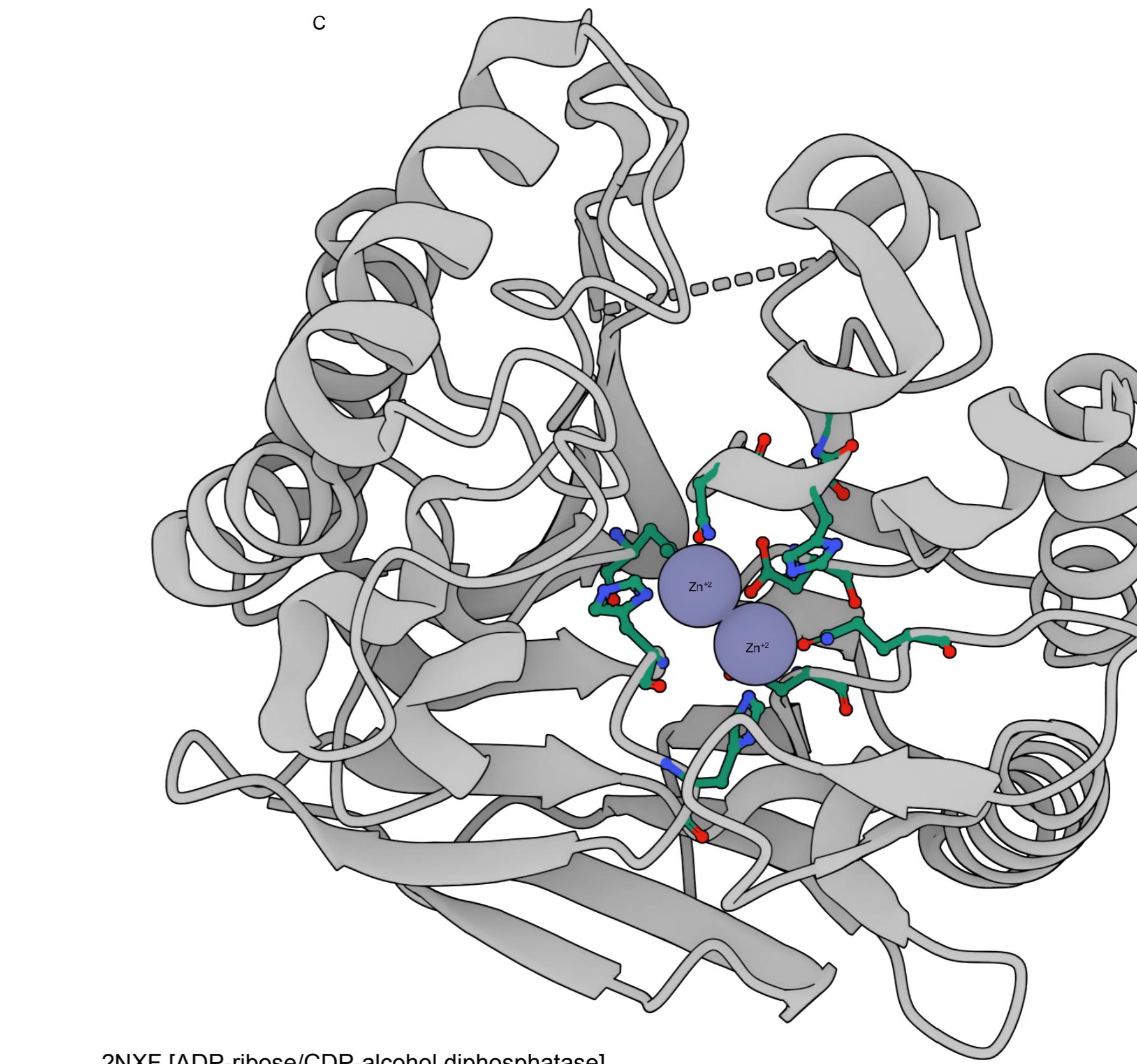
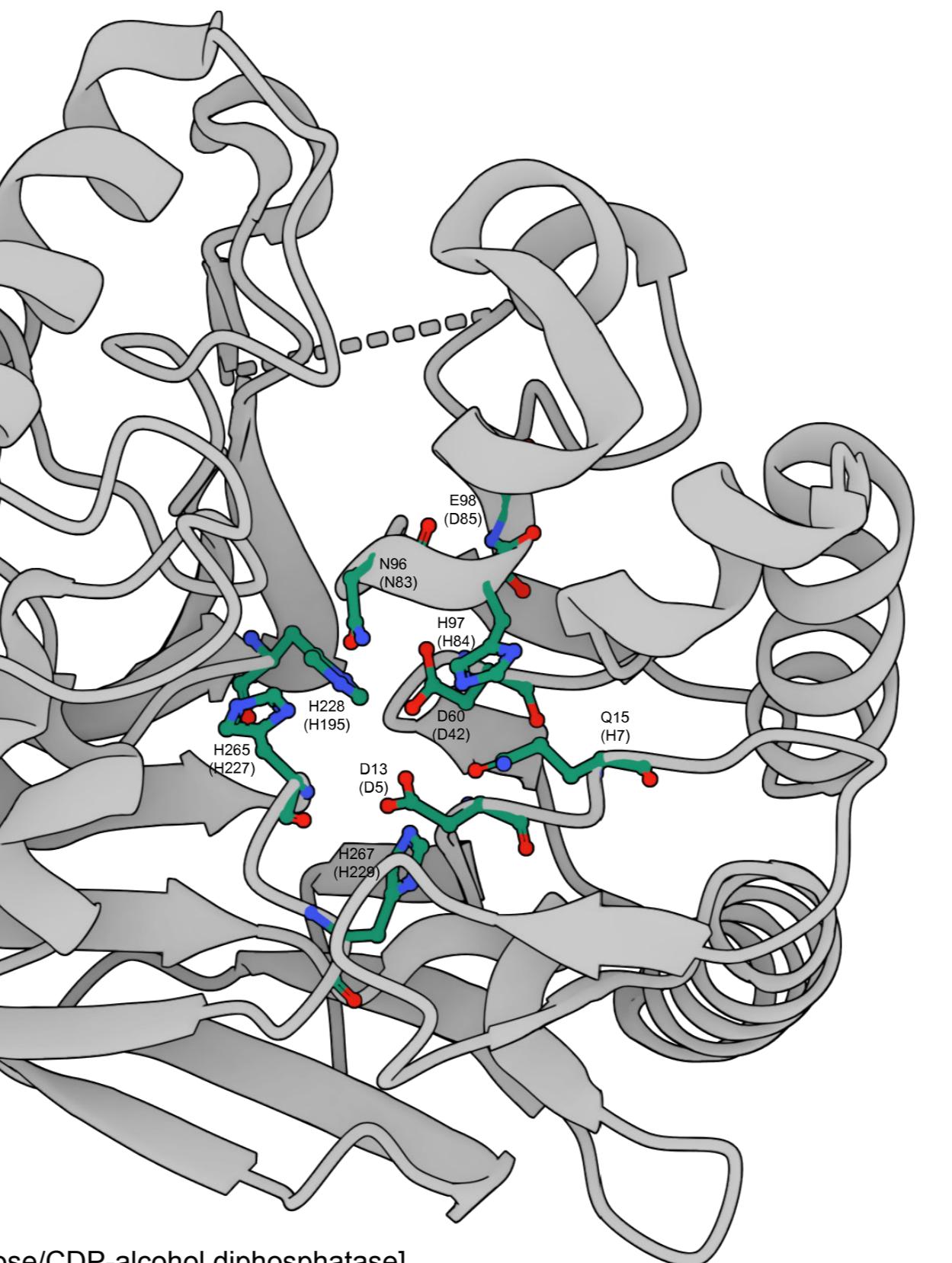
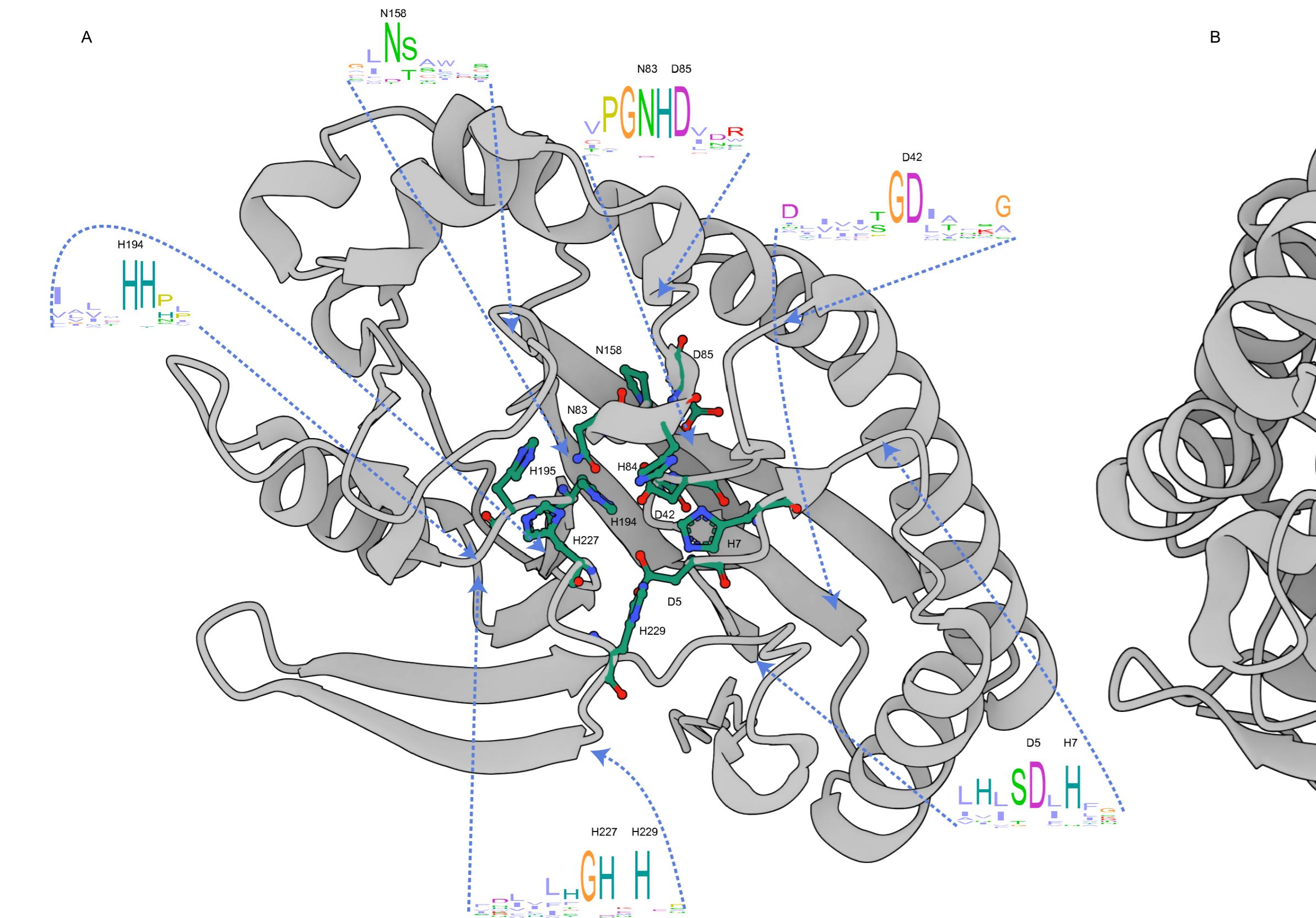
Supplementary figure 2

Supplementary figure 3  
ORC/Cdc6 phylogenetic tree

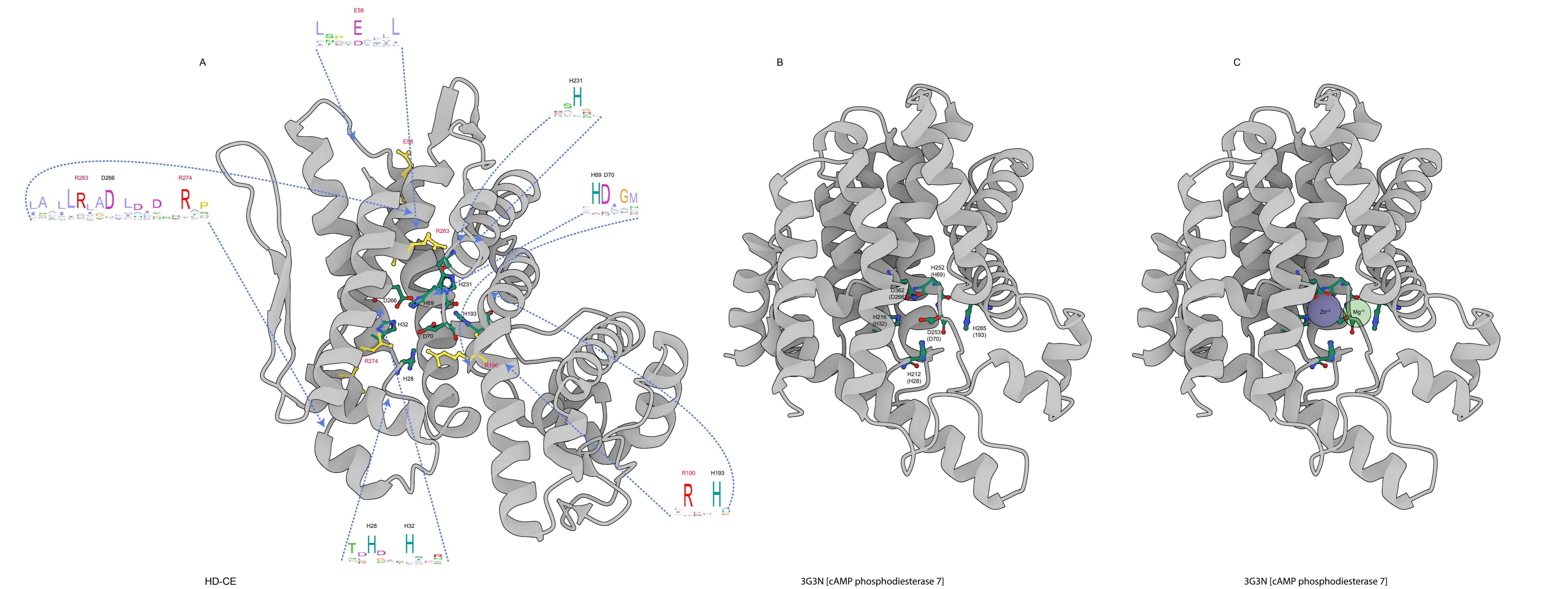




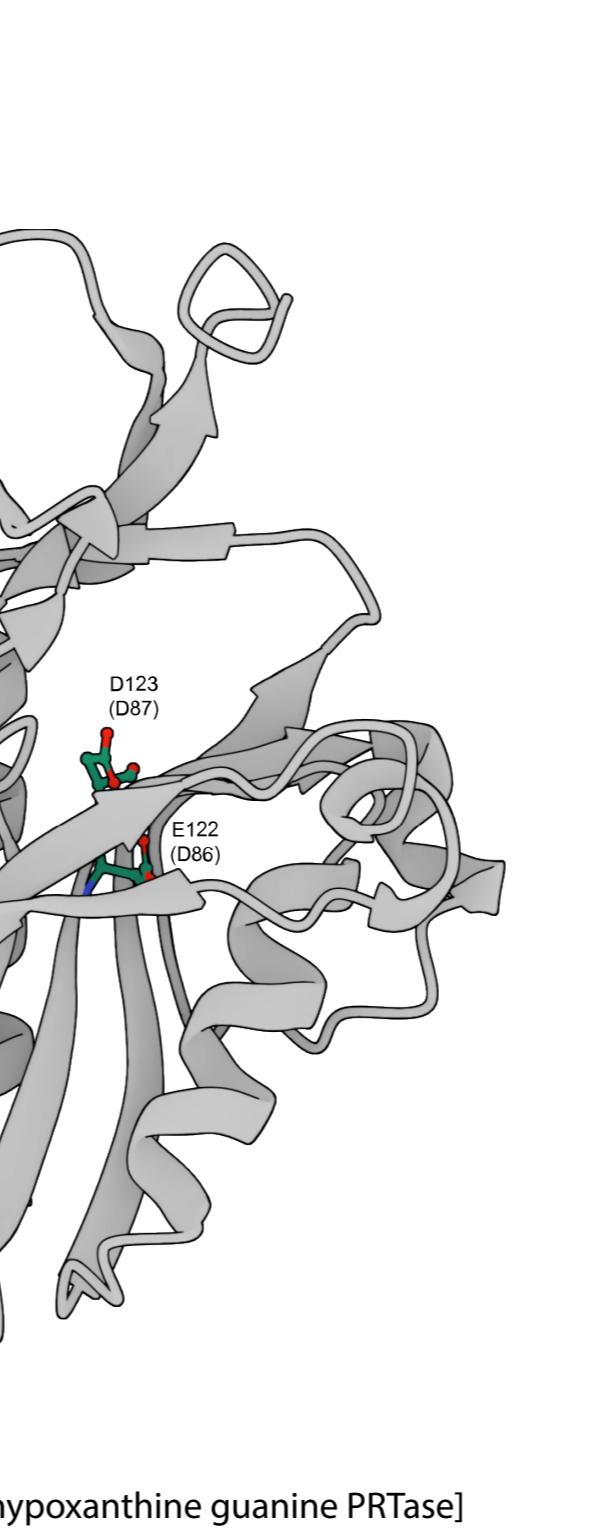
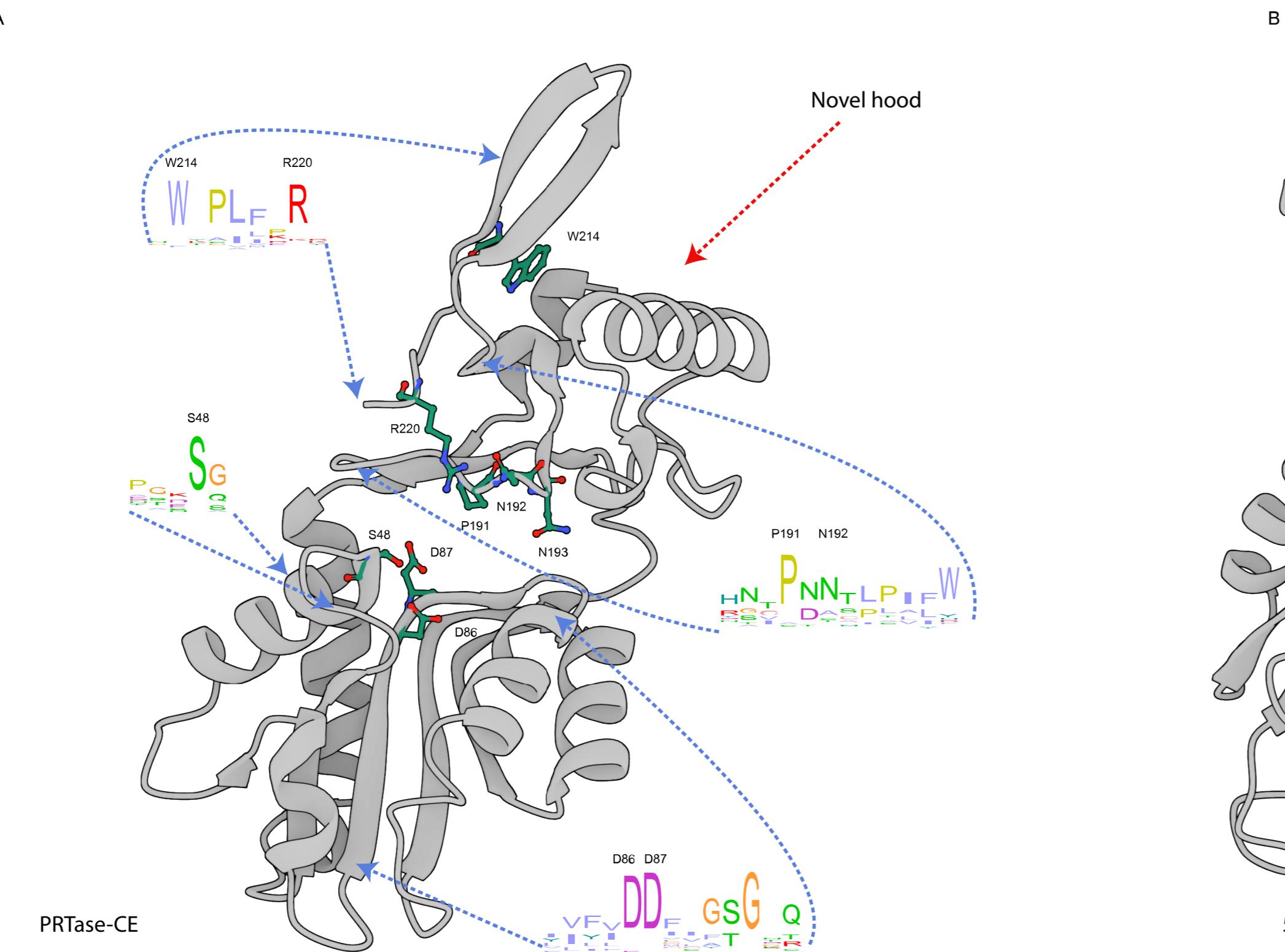
## Supplementary figure 5



Supplementary figure 6



Supplementary figure 7



## Supplementary figure 8

Figure 3A Calcineurin-CE

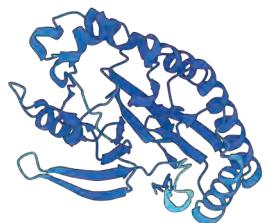


Figure 4G iSirtuin

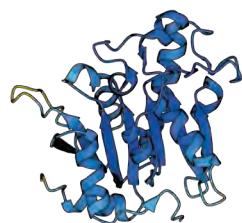


Figure 3B HD-CE

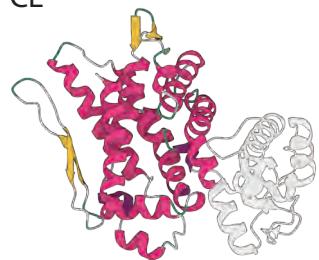
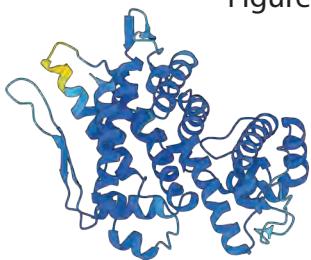


Figure 5G PRTase

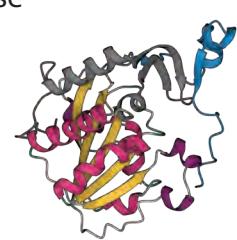
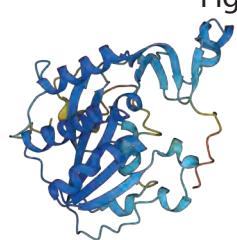


Figure 3C PRTase-CE



Figure 6B HSP90 system with C-terminal wHTH

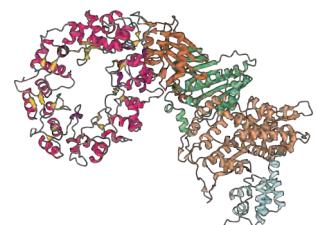
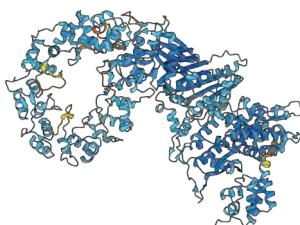


Figure 4B Cdc6-double-CARF•Calcineurin-CE complex

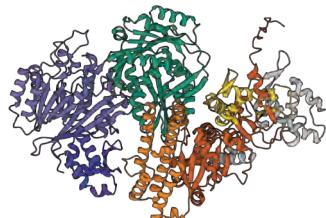
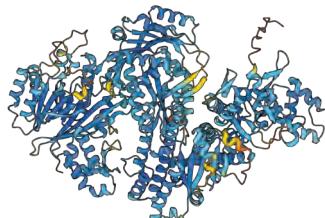


Figure 6E Pepco•Caspase complex



Figure 4D Pua-like

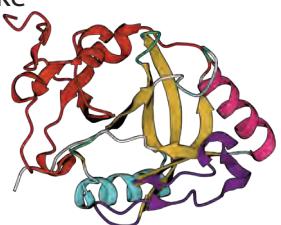
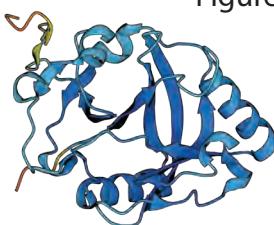
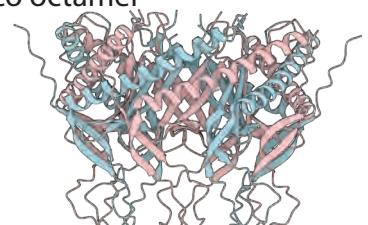
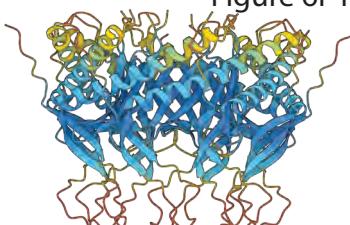


Figure 6F Pepco octamer



■ Very High (pLDDT > 90)

■ Confident (90 > pLDDT > 70)

■ Low (70 > pLDDT > 50)

■ Very Low(pLDDT < 50)













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GCF\_001077193.1 910 HTH+H-CE+HSP90->  
Enterobacter hormaechei  
GCF\_001077193.1 911 HTH+H-CE+HSP90->  
Enterobacter hormaechei subsp. hoffmannii  
GCF\_001077193.1 912 HTH+H-CE+HSP90->  
Enterobacter hormaechei subsp. hoffmannii  
GCF\_001077193.1 913 Ribosomella\_S22->H-CE+HSP90-M->H-CE+HSP90->  
Enterobacter hormaechei subsp. hoffmannii  
GCF\_001077193.1 914 HTH+H-CE+HSP90->  
Enterobacter hormaechei subsp. hoffmannii  
GCF\_001077193.1 915 HTH+H-CE+HSP90->  
Enterobacter hormaechei subsp. hoffmannii  
GCF\_001077193.1 916 HTH+H-CE+HSP90->  
Enterobacter hormaechei subsp. hoffmannii  
GCF\_001077193.1 917 HTH+H-CE+HSP90->  
Enterobacter hormaechei subsp. hoffmannii  
GCF\_001077193.1 918 HTH+H-CE+HSP90->  
Enterobacter hormaechei subsp. hoffmannii  
GCF\_001077193.1 919 HTH+H-CE+HSP90->  
Enterobacter hormaechei subsp. hoffmannii  
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Enterobacter hormaechei subsp. hoffmannii  
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GCF\_001077193.1 922 H-CE+HSP90->  
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GCF\_001077193.1 923 Ribosomella\_S22->H-CE+HSP90-M->H-CE+HSP90->  
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This block contains the full sequence of the RCR-CD6-like gene from the provided FASTA file.








































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