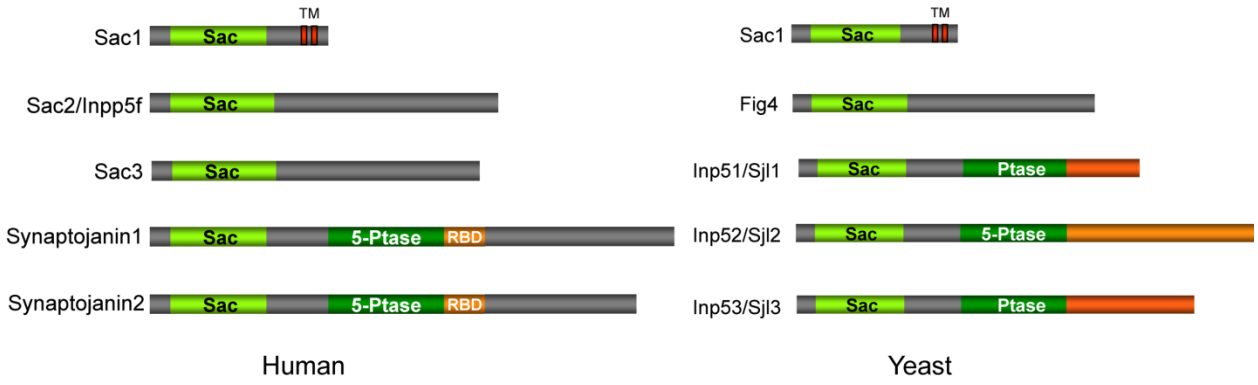
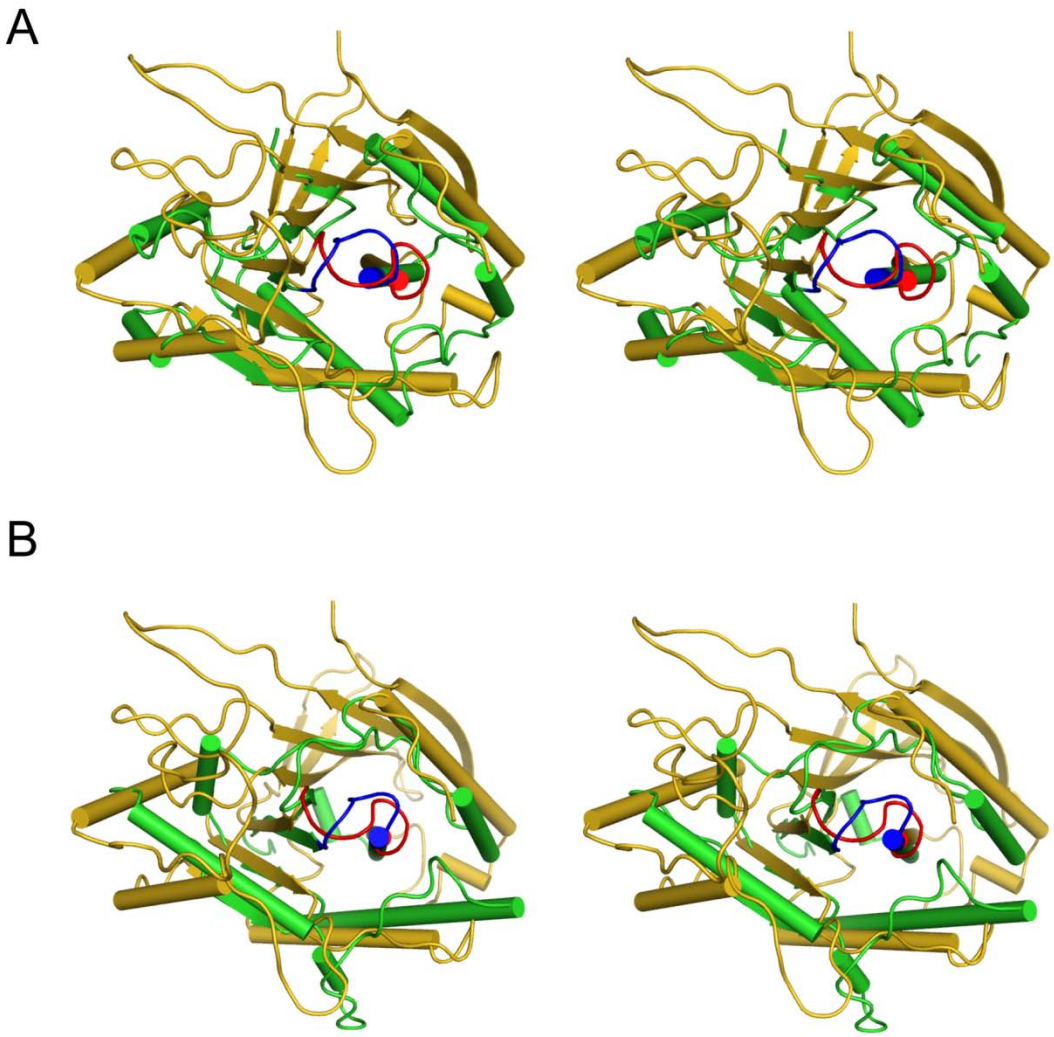
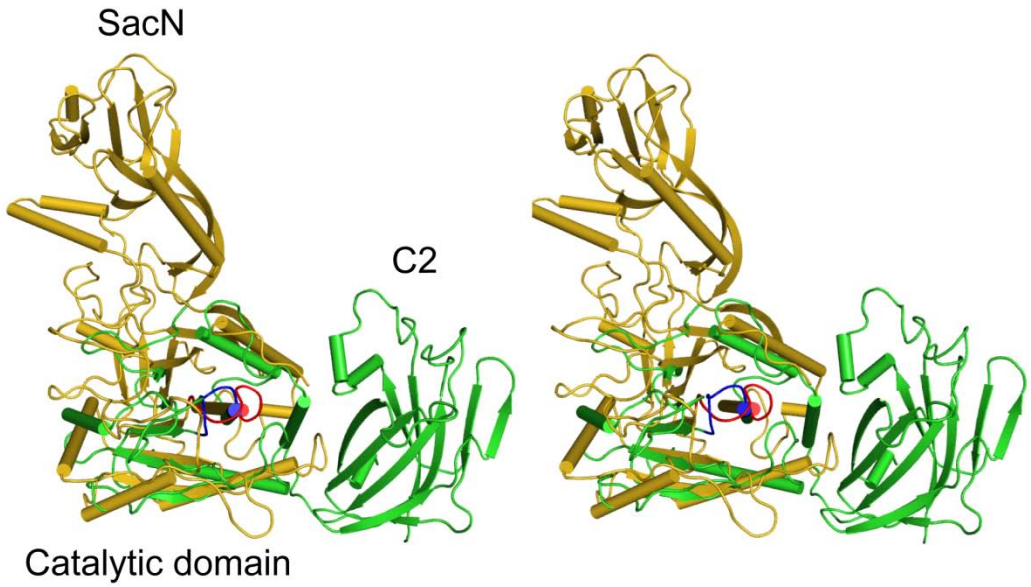
Supplemental Materials:



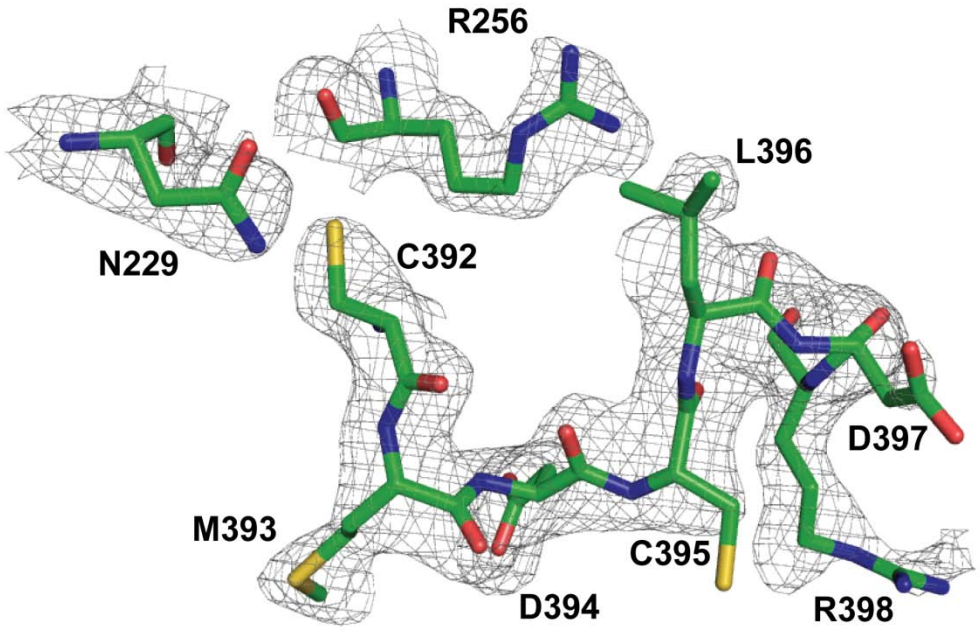
Supplemental Figure 1. Domain Structures of members of the Sac phosphoinositide phosphatase family. Both in human and yeast, there are five proteins contain the Sac phosphatase module. (TM: transmembrane motif; RBD: RNA binding domain)



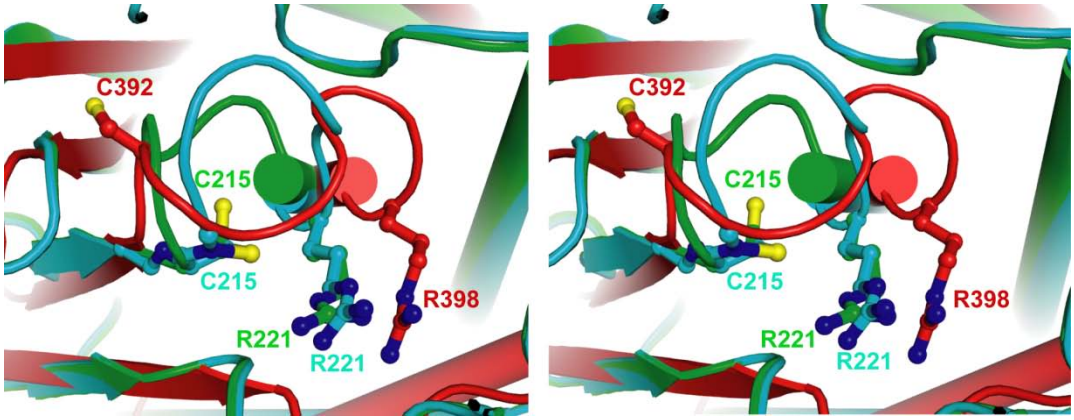
Supplemental Figure 2. Superimposition of the Sac1 phosphatase domain with human PRL-1 phosphatase and HPTP-B. (A) Stereo view of the two overlayed structures of the catalytic domain of Sac1 (yellow) and human PRL-1 (green, PDB ID: 1xm2). (B) Stereo view of the structural superimposition of Sac1 (yellow) and HPTP-B, a human B-form low molecular weight PTP (green, PDB ID: 1XWW). The catalytic P-loops are colored in red for Sac1 and blue for both PRL-1 and HPTP-B.



Supplemental Figure 3. Structural comparison of Sac1 with PTEN. Sac1 is colored in yellow and PTEN is in green. These two structures are superimposed based in structural homology on the catalytic domain. The catalytic P-loops of Sac1 and PTEN are colored in red and blue, respectively. Note that the SacN domain of Sac1 is located on the opposite side of the central β sheet compared to the C2 domain of PTEN.



Supplemental Figure 4. Electron density map (2fo-fc) of the P-loop and residues in close vicinity with the catalytic C392. The map is contoured at 1β level. The electron density for the thiol group of the catalytic residue, C392 is well defined.



Supplemental Figure 5. Structural comparison of Sac1 with canonical PTP1Bs at both reduced and oxidized state. Stereo view of the superimposition of the catalytic region of Sac1 (red) with reduced form of PTP1B (green, PDB ID: 1AAX) and oxidized (cyclic sulphenamide state) PTP-1B (cyan, PDB ID: 1OEM). Note that the conformation of the catalytic P-loop of Sac1 is strikingly different from that of both reduced and oxidized forms of PTP1B. The side chains of the catalytic C392 and the conserved R398 residues in Sac1 are located on the opposite side of the P-loop; while in both reduced and oxidized PTP1Bs, these two residues are on the same side relative to the P-loop.

Supplemental Table 1. Data collection, phasing and structural refinement statistics

A. Data collection and phasing		
Space group	I222	
Cell dimensions	a = 86.2 Å, b = 94.7 Å, c = 155.4 Å, $\alpha = 90^0$, $\beta = 90^0$, $\gamma = 90^0$	
	Se SAD phasing data	Refinement data
Wavelength (Å)	0.9788	0.9789
Resolution (Å)	50-2.20 (2.28-2.20)	50-1.97 (2.04-1.97)
Observed reflections	469,908	649,170
Unique reflections	32,111	45,940
Completeness (%)[a]	100 (100)	99.7 (100)
$\langle I \rangle / \langle \sigma \rangle$[a]	14.5	15.3
R_{sym}[a,b]	0.068(0.371)	0.065(0.729)
Se-SAD FOM	0.184	σ
Se-SAD FOMDM	0.30	σ
B. Refinement		
Resolution (Å)[a]	33-1.97(2.00-1.97)	
R_{crys} / R_{free} (%)[a,c]	20.1/24.2 (25.5/25.9)	
Rms bond length (Å)	0.01	
Rms bond angles (°)	1.2	
Ramachandran plot		
Most favored/Additional (%)	94/6	
Generous/Disallowed (%)	0.0/0.0	

[a]Values in parenthesis are for the highest resolution shell.

[b]$R_{sym} = \sigma_h\sigma_i|I_I(h) - \langle I(h)|/\sigma_h\sigma_i I_I(h)$.

[c]$R_{crys} = \sigma(|F_{obs}|-k|F_{cal}|)/\sigma|F_{obs}|$. R_{free} was calculated for 5% of reflections randomly excluded from the refinement.