MUE 0.8 [95%: 0.7, 1.0] kcal/mol MUE 0.9 [95%: 0.7, 1.2] kcal/mol MUE 0.8 [95%: 0.6, 1.0] kcal/mol 3 2 cycle closure ΔΔG (kcal/mol) cycle closure ∆∆G (kcal/mol) cycle closure ∆∆G (kcal/mol) 2 1 0 -2 0 experiment  $\Delta\Delta G$  (kcal/mol) experiment  $\Delta\Delta G$  (kcal/mol) experiment  $\Delta\Delta G$  (kcal/mol) MCL1 P38 Thrombin RMSE 1.0 [95%: 0.8, 1.2] kcal/mol RMSE 1.4 [95%: 1.2, 1.6] kcal/mol RMSE 0.9 [95%: 0.6, 1.2] kcal/mol MUE 1.2 [95%: 1.0, 1.3] kcal/mol MUE 0.8 [95%: 0.6, 1.0] kcal/mol MUE 0.8 [95%: 0.5, 1.1] kcal/mol cycle closure  $\Delta\Delta G$  (kcal/mol) cycle closure ∆∆G (kcal/mol) cycle closure  $\Delta\Delta G$  (kcal/mol) 1.0 1 0.5 0 0.0 -0.5 -2 -1.0-1.5-2 experiment  $\Delta\Delta G$  (kcal/mol) experiment  $\Delta\Delta G$  (kcal/mol) experiment  $\Delta\Delta G$  (kcal/mol) Tyk2 PTP1B all RMSE 0.9 [95%: 0.7, 1.2] kcal/mol RMSE 1.2 [95%: 0.9, 1.6] kcal/mol RMSE 1.1 [95%: 1.1, 1.2] kcal/mol MUE 0.8 [95%: 0.6, 1.0] kcal/mol MUE 0.9 [95%: 0.7, 1.1] kcal/mol MUE 0.9 [95%: 0.8, 1.0] kcal/mol 2 cycle closure ∆∆G (kcal/mol) cycle closure  $\Delta\Delta G$  (kcal/mol) cycle closure ∆∆G (kcal/mol) 1 0 0 **-**2 -3-2 **-**2 0 -2.50.0 2.5

experiment  $\Delta\Delta G$  (kcal/mol)

CDK2

RMSE 1.1 [95%: 0.9, 1.4] kcal/mol

JNK1

experiment  $\Delta\Delta G$  (kcal/mol)

RMSE 1.0 [95%: 0.7, 1.3] kcal/mol

**BACE** 

experiment  $\Delta\Delta G$  (kcal/mol)

RMSE 1.0 [95%: 0.9, 1.2] kcal/mol