obtained using phosphate buffer (pH 7.0, 1.75Å diffraction, R_{factor}=18%) showed the presence of a bound phosphate anion interacting with His87, a key residue in cluster release (1). The phosphate also interacts with the N-terminus of a symmetry-related dimer (Figure). None of these interactions were previously reported (2-4). We attribute the increased stability to the novel interactions, suggesting that the rate of cluster release could be modulated by interaction with a phosphate or phosphate moiety, such as a phosphorylated protein or peptide.

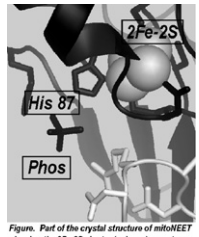

Figure. Part of the crystal structure of mitoNEET showing the 2Fe-2S cluster (spheres), a cartoon representation of the backbone (black is one dimer and white a symmetry related dimer) and specific amino acids (as labeled) that interact with the bound phosphate anion (black tetrahedron).

(1) Wiley *et al.* (2007) *J Biol Chem.* **282**, 23745-23749.
(2) Paddock *et al.* (2007) *Proc Natl. Acad. Sci USA* **104**, 14342-14347.
(3) Lin *et al* (2007) *Proc. Natl. Acad. Sci USA* **104**, 14640-14645.
(4) Hou *et al* (2007) *J Mol Biol* **282**, 33242-33246.
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2283-Pos Board B253
Potent Inhibitors Of c-Myc-Max Dimerization Through Multivalent Binding To The Intrinsically Disordered c-Myc Monomer
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We have shown that selective inhibitors of dimer formation between the oncogenic basic-helix-loop-helix-leucine zipper (bHLHZip) trancription factor c Myc and its bHLHZip partner protein Max act by binding to the intrinsically disordered (ID) c Myc monomer. Multiple, independent sites for inhibitor binding were found along c-Myc bHLHZip. We exploited the multiplicity of these sites to generate novel compounds capable of multivalent binding to c-Myc. Despite their disordered protein target, these molecules bind purified c-Myc with low nano-molar affinity, which is orders of magnitude tighter than that of c-Myc's obligate heterodimerization partner Max. The inhibitors effectively disrupt c-Myc-Max dimerization and specific DNA binding; they also inhibit growth of c-Myc overexpressing cancer cell lines in vitro.

2284-Pos Board B254
Dynamic Analysis of Beta-lactamase Ligand Recognition
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A serious public health threat today is the emergence of pathogens that are resistant to commonly used antibiotics. One of the mechanisms of acquired drug resistance is the bacterial production of beta-lactamases, which break down these antibiotics. Currently used beta-lactamase inhibitors are not effective at targeting the 700 types and new mutants of beta-lactamases. Beta lactamase is therefore an important drug target in combating antibiotic resistance. Beta lactamase inhibitory protein (BLIP) is an effective inhibitor of TEM-1 and SHV-1, but binds and inhibits the two variants with different affinities. We hypothesize that elucidating the mechanism whereby the differential binding results will guide the design of new peptide inhibitors based on the BLIP structure. Molecular dynamics simulations are performed to examine the binding properties of BLIP and BLIP based peptides to TEM-1 and SHV-1 beta lactamase. These simulations on the complex will guide the design of new peptides.

2285-Pos Board B255
The Role Of Dynamics On Binding Specificity And Promiscuity
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Protein - protein interactions regulate and control a wide range of physiological processes. Protein interaction networks abound with proteins that have only a few connections while a small number of proteins, which are called hub proteins, are highly connected. Recent reports suggest that hub proteins are structurally and dynamically different from non-hub proteins. Hub proteins tend to be more disordered than other proteins. Further, binding partners of hub proteins are also observed to have higher levels of disorder. Here we perform a detailed examination of hub and non-hub proteins using the Gaussian Network Model (GNM) to elucidate the role of intrinsic dynamics for binding diversity and promiscuity.

2286-Pos Board B256
Phospho(enol)pyruvate Binding to Thermus thermophilus Phosphofructokinase
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ATP-dependent type 1 prokaryotic phosphofructokinase (PFK) catalyzes the conversion of fructose-6-phosphate (F6P) and MgATP to fructose-1,6-bisphosphate and MgADP. This enzyme is allosterically inhibited by phosphoenolpyruvate (PEP) and exists as a homotetramer with the four active sites formed along one dimer-dimer interface and four allosteric sites formed along the other. The overall structures of PFK's from E. coli, Bacillus stearothermophilus, and Lactobacillus delbruekii are very similar, and the sequences have high percent identity and similarity with Thermus thermophilus PFK. Thermus thermophilus PFK (TtPFK) comes from a gram negative bacterium that is an extreme thermophile. One of the interesting features of TtPFK is an unusually tight PEP binding (Kd=1.3 ± 0.02mM at 250C pH 8) compared to PFK's from E. coli (300 ± 10mM), Bacillus stearothermophilus (60 ± 4mM), and Lactobacillus delbruekii (24 ± 2mM). Since no structural data are available for TtPFK to date, a structure of a highly homologous PFK from a moderate thermophile Bacillus stearothermophilus was used to predict the residues important for PEP binding. From the sequence alignment and the PEP-bound D12A BsPFK structure, three non-conserved residues were identified in the allosteric binding site that may be responsible for tight binding: R55, N59, and S215. To quantify the contribution of these residues to PEP binding, single and double mutations were made to the corresponding residues in BsPFK, EcPFK, and LbPFK. Kinetic data showed that these mutations weakened the binding of PEP to different extents. In case of N59D/S215H, the PEP binding affinity was 10-fold lower N59D showed a 100-fold decrease in PEP binding affinity and R55G showed a 700-fold decrease in PEP binding. Furthermore, these mutants showed a slight increase in coupling, which means that although the binding of PEP becomes weaker, its ability to inhibit was somewhat improved. Supported by NIH grant GM33261 and Welch Foundation grant A1543.

2287-Pos Board B257
Distinguishing Interactions Responsible for Phospho(enol)pyruvate Binding from Interactions that Communicate Allosteric Inhibition in E. coli Phosphofructokinase
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The notion that substrate affinity is modified via interaction of effector ligands is a fundamental characteristic of allostery. In order to further understand the complexities of this phenomenon, this study investigates the role that functional groups in phospho-enol-pyruvate PEP play in ligand binding and allosteric propagation. Thermodynamic linkage analysis enables the nature and magnitude of allostery to be determined, allowing allosteric action to be distinguished from allosteric ligand binding affinity. By using this type of analysis to compare the inhibition caused by PEP to the inhibition imposed by PEP analogs upon binding to E. coli PFK (EcPFK), the importance of specific functional groups of PEP to ligand binding and/or allostery can be ascertained. EcPFK displays a much weaker binding affinity for the PEP analog phosphoglycolate (PG) compared to PEP. However, PG is still able to inhibit EcPFK to an extent comparable to that of PEP. This finding suggests that the methylene group that is absent in PG plays a larger role in ligand binding than in allosteric propagation. The chemical structure of phosphonoacetic acid (PA) is very similar to that of PG except for the deletion of the oxygen that bridges the phosphate group to the rest of the molecule. When the inhibition of EcPFK by PA is examined, a binding affinity comparable to PG is observed but a substantial loss in allostery is also observed. These data suggest that the bridging oxygen in PEP contributes substantially to the propagation of allosteric signal. Funding is provided by NIH grant GM33261 and Welch Foundation grant A1543.

2288-Pos Board B258
Weak Binding of Phospho(enol)pyruvate to Phosphofructokinase from Lactobacillus delbrueckii
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Most prokaryotic phosphofructokinases (PFKs), like those from Bacillus stearothermolphilus (BsPFK) and E.coli (EcPFK), exhibit both tight binding affinity for the allosteric inhibitor phosphoenolpyruvate (PEP) and strong inhibition. PFK from Lactobacillus delbrueckii subspecies bulgaricus (LbPFK), which is similar in structure and sequence to BsPFK and EcPFK, exhibits weak PEP binding, with the strength of the inhibition being indeterminate. D12, found along the active site interface, is conserved in over 150 prokaryotic PFKs,