This suggests that chloroquine and NADH are competitive inhibitors for this particular enzyme. In this study, molecular docking was used to determine and explore potential binding of chloroquine to *Plasmodium falciparum* glyceraldehyde-3-phosphate dehydrogenase (pfGAPDH), another glycolytic enzyme that shares a common cofactor with LDH. Automated docking using Autodock 4.2 was employed to determine binding sites and binding energies of chloroquine docked to monomeric and tetrameric forms of pfGAPDH with and without the cofactor present.
Docking solutions for the monomer revealed two binding sites for chloroquine, one of which was the cofactor binding pocket. In the absence of NADH, 61 % of conformations with sufficiently low binding energy were located in the NADH binding pocket (average binding energy of -5.943 ± 0.085 kcal/mol) with 31% in the secondary binding site (average binding energy of -4.937 ± 0.025 kcal/mol). With the cofactor present, the secondary binding pocket accounted for 100% of stable complexes with an average binding energy of -4.803 ± 0.015 kcal/mol. With the tetramer, the most stable complexes were found in a new hydrophobic pocket at the interface between the subunits with 56% and 80% favorability in the absence and presence of cofactor, respectively.

2128-Pos Board B114
Optimization of a BCL6 Inhibitor using the Site-Identification by Ligand Competitive Saturation (SILCS)
Wenbo Yu, Alexander D. MacKerell, Jr.
Fragment-based drug design has developed significantly over the past ten years and is now recognized as a successful method of lead compound generation and optimization[1]. Computational approaches to fragment-based drug discovery have the potential to dramatically mitigate the costs of experimental based approach. However, the majority of computational methods suffer from limited representation of protein flexibility and solvation effects. Recently, a fragment-based approach based on explicit solvent all-atom molecular dynamics simulations (SILCS: Site Identification by Ligand Competitive Saturation) was developed in our lab to overcome these drawbacks[2]. As a test case, we applied this method to the BTB domain of BCL6 protein. Good agreements between calculated three-dimensional probability maps of fragment binding and the X-ray structure of the BCL6 inhibitor 79-6[3] were found. In addition, a more specific SILCS simulation was performed and several potential functional group binding sites around the location of 79-6 were identified. Based on the location of these functional groups, modifications of 79-6 were proposed. Free energy perturbation (FEP) calculations, including FEP using the orthogonal space random walk (OSRW) approach[4], were applied to obtain quantitative computational estimates of the relative free energy of binding associated with these modifications. Two FEP methods show consistent results that the modified compound has higher binding affinity to BCL6 than parent compound 79-6. This result indicates that the SILCS method has the ability to qualitatively inform the optimization of small-molecule inhibitors.
[1] Schulz, M.; Hubbard, R. Curr. Opin. Pharmacol. 2009, 5, 615.
[2] Guvench, O.; MacKerell, A. D., Jr. PLoS Comput. Biol. 2009, 5, e1000435.
[3] Cerchietti, L. C.; Ghetu, A. F.; Zhu, X. and et al. Cancer Cell 2010, 17, 1.
[4] Zheng, L.; Chen, M.; Yang, W. Proc. Natl. Acad. Sci. U.S.A. 2008, 105, 20227.

2129-Pos Board B115
Exploring New Druggable Binding Sites of Platelet Integrin αIIbβ3
Ana Negri, Sarasija Naini, Barry S. Coller, Marta Filizola.
The major ligand binding site of platelet integrin alphaIIbbeta3, an essential receptor for hemostasis and thrombosis, lies between the head regions of its alpha and beta subunits. The Arginine-Glycine-Aspartic Acid (RGD) cell attachment sequence mediates the binding of several different adhesive plasma proteins to integrin alphaIIbbeta3. This sequence binds to both alphaIIb and beta3 residues in the ligand binding pocket, as well as to a divalent metal ion contained in the beta3 subunit. We recently identified a novel alphaIIbbeta3 antagonist (RUC-1) that binds exclusively to alphaIIb. In the present study we searched for additional new druggable binding sites of the integrin alphaIIbbeta3 headpiece along the conformational transition between its closed and open (swung-out) conformations. Specifically, we considered ten different alphaIIbbeta3 conformations resulting from a linear interpolation between the two extreme conformations of alphaIIbbeta3, and relaxed them by multi-nanosecond molecular dynamics simulations. Each trajectory was clustered by root mean square deviation over the protein Calpha atoms, and each cluster medoid was used as an input to a recent energy-based mapping algorithm (FTMAP) that searches an entire protein surface for consensus binding regions for a number of small organic probe molecules. Our results reveal new pockets at the beginning of the conformational transition whose structural information might be used as the basis for rational drug design of novel therapeutics targeting integrin alphaIIbbeta3.

2130-Pos Board B116
A New Class of Lipidic Immunomodulators that Activate TLR-Dependent Cascades and Cytokine Secretion
Caroline Lonez, Michel Vandenbranden, **Jean-Marie Ruysschaert**.
Cationic lipids are positively charged amphiphilic molecules which, for most of them, form positively charged liposomes, sometimes in combination with a neutral helper lipid. Such liposomes are mainly used as efficient DNA, RNA or protein carriers for gene therapy or immunization trials. Over the past decade, significant progress has been made in the understanding of the cellular pathways and mechanisms involved in lipoplex-mediated gene transfection (1) but the interaction of cationic lipids with cell components and the consequences of such an interaction on cell physiology remains poorly described. Recently, trying to explain the immunoadjuvant properties (2) of a cationic lipid discovered in our group (N-t-butyl-N'-tetradecyl-3-tetradecylamino-propionamidine-diC14-amidine), we identified its agonistic interaction with the Toll-like receptor 4 (TLR4), the natural sensor of LPS (the bacterial lipopolysaccharide). This activation seems specific of the shape and characteristics of the molecule since increasing the length of the hydrocarbon chains by 2 methyl groups suppresses its activity. This cationic lipid has only limited features in common with LPS species from different bacterial origin such as short hydrocarbon chains and the presence of a polar headgroup. However, the number of chains (2 versus generally 6 to 7) and the polar headgroup (small alkylated cationic amidinium group versus the bulky polar anionic headgroup of LPS) make the two molecules look very different but surprisingly such dissimilar structures are capable of activating the same receptor(3). As compared with other adjuvants being currently developed, the chemistry of amidine derivatives is rather simple, allowing the quick development and screening of new derivatives.
1- Mol Ther. (2005) −11(3):336-47
2- Mol Ther. (2005) 11 (6), 960-968
3- Prog Lipid Res. (2008) 47(5):340-7

2131-Pos Board B117
Local Protein Surface Patch Method for Protein-Ligand Binding Prediction
Lee Sael, Daisuke Kihara.
Characterizing the protein structures of an unknown function is an important task in bioinformatics. Function of a protein, specifically, the type of ligand that bind to a protein, can be predicted by finding similar local surface regions of known proteins. Unlike existing methods that compare the global characteristics of a protein fold, we propose a local surface-based approach which can find functional similarity between non-homologous proteins. In the proposed pocket comparison method, the pockets are segmented to surface patches, which are then compared using a modified weighted bipartite matching algorithm. The 3D Zernike descriptors, which have been found to be successful in representing protein global surface properties (Sael L, Li B et al. Proteins, 2008; Sael L, La D et al. Proteins, 2008) and global pockets shape comparison (Chikhi R et al. Proteins, 2010), are used to encode the geometric and physicochemical properties of the surface patches. By representing a pocket by a set of local patches, local similarity of binding pockets can be captured. This is effective when pocket shapes are slightly different due to flexibility of ligand molecules. The binding ligand prediction performance was evaluated on a data set of 100 non-homologous proteins that bind to either one of nine types of ligands. 84.0% of the binding ligands were predicted correctly within the top three scores using the shape and pocket size information, which is better than the previous method which uses the surface of whole pocket. The performance was further improved to 87.0% when surface properties, i.e. electrostatic potential and hydrophobicity, were added. Overall, we show that proposed method is powerful in predicting the type of ligand a protein binds even in the absence of homologous proteins in the database.

2132-Pos Board B118
A Novel Method for Guiding Protein-Ligand Docking with QSAR-Derived Pharmacophore Maps
Sam DeLuca, Jens Meiler.
Currently, QSAR and computational ligand docking studies are valuable but independently used tools for drug design. Data from Pharmacophore maps produced by tools such as COMFA are typically compared to the results of docking simulations by hand in a qualitative manner. RosettaLigand has been previously successful at predicting binding poses with high resolution resolution (Kaufmann, et. al, Proteins, 2009). We are developing RosettaHTS, an extension to RosettaLigand which will integrate these two methods by using information from QSAR derived pharmacophore maps to guide the low resolution phase of ligand docking. Pharmacophore maps are generated using