SESSION: COMPUTATIONAL BIOLOGY, BIOINFORMATICS, BIOCHEMISTRY, AND BIOPHYSICS (BIO)

INVITED SPEAKERS

BIO-I-01

Structure based drug design of histone deacetylase inhibitors: lessons learned from computational studies and X-ray crystallography

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ABSTRACT

***Keywords**: Epigenetics, Drug Design, Histone Deacetylases, Docking, Molecular Dynamics*

Histone deacetylases (HDACs) are important modulators of epigenetic gene regulation and additionally control the activity of non-histone protein substrates. While for HDACs 1-3 and 6 many potent selective inhibitors have been obtained, for other subtypes much less is known on selective inhibitors and the consequences of their inhibition. In the present talk the structure based design of isoform selective HDAC inhibitors will be discussed. Docking studies using available crystal structures have been used for structure-based optimization of several series of compounds. We have investigated the role of HDAC6, HDAC8 and HDAC10 in the proliferation of cancer cells and optimized hits for potency and selectivity, both in vitro and in cell culture.1-3 The combination of structure-based design, synthesis, in vitro screening to cellular testing resulted in potent and selective HDAC8 inhibitors that showed anti-neuroblastoma activity in cellular testing.1,2 A second project focused on the development of isoform specific inhibitors of parasitic HDACs. Structure based design and crystallization resulted in the development of Schistosoma mansoni HDAC8 inhibitors for the treatment **of** bilharzia.4-6 In the present talk results from the computational studies including large ligand docking and molecular dynamic simulations are presented and discussed in the context of the obtained crystal structures of HDAC-inhibitor complexes.

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BIO-I-01

Wolfgang Sippl got a PhD in Pharmaceutical Chemistry at the University of Duesseldorf and was a post-doctoral fellow at the Universite Louis-Pasteur in Strasbourg (France). He was a full professor for Medicinal Chemistry, University of Halle-Wittenberg in 2003. Since 2010, he is a director of the Institute of Pharmacy in Halle. His main interests are computational chemistry and structure-based drug design.

BIO-I-02
Theoretical analyses on membrane permeability

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ABSTRACT

***Keywords**: Molecular Dynamics Simulations, Drug Design, Membrane Permeability, LogP*

In recent years, middle-sized molecular drugs have attracted much attention from both industrial and pharmaceutical views in drug discovery because they possess advantages of both small drugs and antibodies. However, the physical properties of cyclic peptides have not been sufficiently understood. For example, there is no evaluation list on membrane permeability, and thus ADME has not been established. Therefore, it is worth investigating the membrane permeability of these molecules by theoretical methods. One of the alternative physical quantities for estimating the membrane permeability is a partition coefficient between octanol and water, log$P_{o/w}$, which is calculated by the following equation.

$$\log P_{o/w} = \frac{\Delta G_{wat} - \Delta G_{oct}}{2.301RT}$$

where ΔG_{wat} is the solvation free energy for water, ΔG_{oct} is that for n-octanol, R is the gas constant, and T is the absolute temperature. Approximately 200 compounds, mainly low- to medium-molecular-weight organic compounds, were calculated using the *ab initio* and semiempiricalmethods with the self-consistent reaction field (SCRF) method with Gaussian16 [1]. Using the PM7/SMD and multi-regression method, we have achieved a good correlation between experimental and calculated log$P_{o/w}$, values [2].

Also, we have performed target molecular dynamics (tMD) simulations during membrane permeation processes using NAMD [3]. The target molecule used here is the syringolin A (SylA) and derivatives, which have a 12-membered cyclic peptide and exhibit weak proteasome inhibitory activity. In these simulations, the artificial force was applied to the center-of-mass of the chain. For each molecule, three trials were conducted from different initial conditions. The probability of membrane permeation was measured by changing the magnitude of the force in the range from 1 nN to 2 nN in tMD. We qualitatively confirmed the differences in permeation behaviors of three SylA derivatives, which is consistent with the experimental results.

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BIO-I-02

Yasuteru Shigeta, a Theoretical Chemist and Biophysicist, graduated from Department of Chemistry, Osaka University and obtained a Doctor of Science degree at there in 2000. He joined University of Tsukuba as a full professor since 2014. He has published more than 240 scientific papers and received several awards, especially, Ministry of Education, Culture, Sports, Science, and Technology (MEXT) Japan in 2010.

BIO-I-03

Second Coordination Effects in Blue Copper Protein with Combined Experimental and Computational Chemistry

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ABSTRACT

***Keywords**: Noncovalent weak interactions, X-ray crystallography, XAS, DFT, QM/MM*

Noncovalent weak interactions (< 10 kJ/mol) originated from the dispersion force have been recognized as important factor in many biological systems[1]. The effects of second coordination sphere on the tuning of active site were studied in a blue copper protein, pseudoazurin (PAz). The electrospray mass spectrometry and circular dichroism spectroscopy showed the stability of Met16 variants differ significantly due to the noncovalent weak interaction in second coordination sphere (Figure 1)[2,3]. The S and Cu K-edge XAS aided by computational simulations of Met16 variants showed that the Cu-S(Cys78) covalency is well correlated with the spectroscopies of type 1 copper site[4]. The high-resolution crystal structure analyses identified S-π/CH-π interaction in wild type PAz, face-to-face/face-to-edge π-π interaction in Met16Phe variant, double CH-π interaction in Met16Leu, and single CH-π interaction in Met16Val and Met16Ile variants in the second coordination sphere. The computational chemistry simulations clarified these interactions with QM/MM (ONIOM) models. The energetic difference of noncovalent weak interaction clarified the structural stability, electronic structure and spectroscopic properties of PAz through the S-π, π-π, CH-π noncovalent weak interactions.

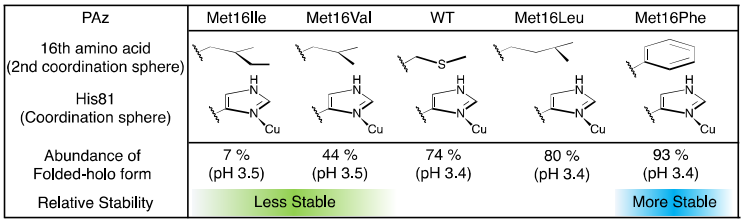

Figure 1. The noncovalent weak interactions in the second coordination sphere in function with the structural stability (abundance of folded-holo form in pH 3.4-3.5)

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Takahide Yamaguchi received his PhD degree from Ibaraki University in 2016. Currently he is an Asst Prof in Ibaraki University. His research interests focus on metalloproteins

BIO-I-03

BIO-I-04

Computational prediction and interpretation of anticancer activities of peptides using a flexible scoring card method

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ABSTRACT

Keywords: *anticancer peptide; peptide; flexible scoring card method; propensity score; machine learning.*

In this study, we develop and propose a flexible scoring card method (FSCM) with estimating propensity scores of local and global sequential information for the development of a sequence-based anticancer peptide (ACP) predictor (named iACP-FSCM) in order to improve the prediction performance and model interpretability [1]. Specifically, the FSCM method is employed to further improve the prediction accuracy and interpretability by utilizing both local and global sequential information of peptides. Both cross-validation and independent tests results revealed that the local sequential information played a crucial role in distinguishing ACPs from non-ACPs than that of the global sequential information. By comparing the iACP-FSCM and the state-of-the-art ACP predictors, we demonstrated that iACP-FSCM was the most suitable choice for ACP identification and characterization considering its simplicity, interpretability and generalizability. It is highly anticipated that the iACP-FSCM may be a useful tool for the rapid screening and identification of promising ACPs for clinical use. Due to the high potential of the FSCM method developed herein, this method could be easily applied for predicting and characterizing other antimicrobial peptides without any major modifications, such as antiviral peptides [2, 3] and antihypertensive peptides [2, 3], hemolytic peptides [4].

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BIO-I-04

Watshara Shoombuatong is an assistant professor in Center of Data Mining and Biomedical Informatics, Mahidol University. He has a specialty in QSAR modelling, machine learning, data mining, bioinformatics and computational biology, and protein and peptide sequence analysis. He is motivated to design and develop cutting-edge computational algorithms, models and pipelines in drug discovery and development.

BIO-I-05
Multiscale Simulations for Covalent Drug Design

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ABSTRACT

***Keywords**: Multiscale simulations, QM/MM, Drug Design*

Quantum mechanical/molecular mechanical (QM/MM) multiscale approach is a well-established computational methodology for investigating biochemical reactions occurring in enzymes. From a drug discovery perspective, a detailed understanding of enzyme catalysis is fundamental to assist the design of covalent inhibitors targeting enzyme residues essential for the catalytic functioning.[1]

In the present talk, we summarize our experience in the field of QM/MM simulations applied to drug design problems which involved the optimization of compounds inhibiting well-known drug targets, including fatty acid amide hydrolase (FAAH), monoglyceride lipase (MGL), and epidermal growth factor receptor (EGFR). In this context, QM/MM simulations gave valuable information in terms of geometry (i.e., of transition states and metastable intermediates) and reaction energetics that allowed to correctly predict inhibitor binding orientation[2] and substituent effect on enzyme inhibition.[3] What is more, enzyme reaction modelling with QM/MM provided insights that were translated into the synthesis of new covalent inhibitors featured by a unique combination of intrinsic reactivity, on-target activity, and selectivity.

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BIO-I-05

Alessio Lodola received his PhD from the University of Pavia, in 2005. After a stint at the University of Bristol (UK), Dr. Lodola returned to Italy where he is now Associate Professor of Medicinal Chemistry at the University of Parma. Dr. Lodola's research focuses on the use of multiscale simulations for the design of endocannabinoid modulators, EGFR covalent inhibitors, and Eph-ephrin antagonists.

ORAL PRESENTATION

BIO-O-01

Utilizing temperature and relative humidity data in forest restoration's success evaluation

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ABSTRACT

Keywords: *Forest restoration, Data logger, Weather data*

Forest restoration program has performed at Mae Sa Valley, Chiang Mai for more than 20 years. However, only few studies about the restoration's success were done in this site. In this study, we evaluated the success of tropical montane forest restoration using temperature and relative humidity data. For this purpose, data loggers were installed in three different plantations: natural regeneration site, restoration plantation, and community area. Although all three plantations have similar time series data pattern, but natural regeneration site and restoration plantation can be distinguished from community area by histogram and correlation analysis results. In conclusion, our method can be used as an aspect to evaluate the success of forest restoration program.

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BIO-O-02

Molecular Dynamics and Virtual Screening Study for MCR-3 Inhibitors

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ABSTRACT

Keywords: *Mobile colistin resistance, Colistin, Pyrazolone, Molecular dynamics, Screening*

The polymixin colistin is a last line antibiotic against extensively-resistant Gram-negative bacteria for dangerous type of superbug which was used to treat multidrug resistance. The positively charged colistin bound to negatively charged lipid A can disrupt the Gram-negative bacteria outer cell membrane. To against with colistin, mobile colistin resistance gene (*mcr* gene) which is a plasmid-mediated colistin resistance mechanism has been reported that MCR acts as phosphoethanolamine (PEA) transfer reaction to lipid A on the Gram-negative bacterial outer membrane which neutralizes the negative charge on bacterial membrane and reduces the colistin binding. This consequently causes the bacteria resistance to colistin. In this study, *mcr-3* gene isolated pathogenic *Escherichia coli* strains from pig affect to efficiency of colistin. Molecular dynamic simulation showed H380 and H463 with different protonation state have effect with water accessibility. For screening test, only 8 μg/ml of the parazolone derivative compounds combine with colistin can reduce 50% colistin concentration in strain containing *mcr-3* gene comparing with strain without *mcr-3* gene. Their docking results show sharing residue interaction. Especially, T277 as a donor atom for phosphate oxygen of PEA (MCR-3 substrate). Blocking pore in the active site by pyrazolone compounds with having T277 interaction could be able to inhibit MCR-3 function.

BIO-O-03
Development of a Genetically Integrated PBPK Model for Predicting Uric Acid Homeostasis in Humans

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ABSTRACT

***Keywords**: Physiologically based pharmacokinetic modeling, Single nucleotide polymorphism, Uric acid homeostasis*

Uric acid is one of the vital components that ensure the proper function of our body. Serum uric acid balance is regulated mainly by the secretion and reabsorption by the kidneys. However, much of this process is still hard to accurately simulate. Particularly, genetic variation that can affect uric acid homeostasis [1] has not been incorporated into the modeling of the human kidneys before. Here, we have developed a system of equations to study the human uric acid homeostasis using the physiologically based pharmacokinetic (PBPK) model. The PBPK model incorporates blood flow and tissue composition of organs to describe how uric acid is distributed within the body. We have also implemented the concept of sub-compartments within the kidneys [2] that allows the model to incorporate the genetics of individual patients. We chose to model patients with single nucleotide polymorphisms (SNPs) on the *SLC2A9* gene because the gene variation directly affects the amount of uric acid excreted and reabsorbed by the kidneys [3]. The end product of this research can result in a framework for implementing genetic values as a subsystem while giving way to a better representation of human physiology in highly complex systems.

BIO-O-04
Can SARS-CoV Neutralizing Antibodies Repurpose to SARS-CoV-2 Infection?

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ABSTRACT

Keyword: *COVID-19, SARS-CoV-2, neutralising antibody, MD simulation, binding free energy calculation*

The current pandemic crisis caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has received significant attention worldwide. The treatment by drug, Remdesivir is currently the only antiviral drug that is approved by the FDA for the treatment of COVID-19 and others antiviral drugs are recommended by COVID-19 Treatment Guidelines Panel (the Panel). Moreover, WHO also recommends vaccines for emergency use such as the Pfizer/BioNTech vaccine and AstraZeneca/Oxford-developed vaccines. The antibody-mediated humoral response is crucial for preventing viral infections. In this study, the previously reported neutralising antibodies to SARS-CoV, including m396, 80R, F26G19, and S230 were chosen to investigate their function as neutralising antibodies to SARS-CoV-2. The binding interactions of protein-protein complexes were explored using all-atom molecular dynamics (MD) simulations and solvated interaction energy-based binding free energy (ΔG_{bind}) calculations. In comparison to CR3022 of SARS-CoV-2 neutralising antibodies, m396 and 80R were given lower ΔG_{bind} than CR3022, the different values were 0.77 kcal/mol and 0.62 kcal/mol, respectively. So, neutralising antibodies m396 and 80R might be able to bind to the SARS-CoV-2 receptor binding domain (RBD) better than the remaining studied antibodies and CR3022. This may be suggested that neutralising antibodies of SARS-CoV can act as neutralising antibodies to SARS-CoV-2. Therefore, the obtained information can be useful for further design of novel neutralising antibodies, which are crucial for vaccine-mediated protection against viral infection and ultimately reverse the pandemic.

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BIO-O-05
Claudin-1 as a target for treatment of colorectal cancer

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ABSTRACT

Keywords: *metastatic colorectal cancer, Claudin-1, antibody, molecular dynamics simulation*

Metastatic colorectal cancer (mCRC) is a major cause of cancer-related deaths. To inhibit cancer progression, targeted therapies is used to directly inhibit molecules involving in tumorigenesis. Claudin-1 (CLDN1, Fig. 1A) is one of the attractive molecular targets for cancer therapy. It is overexpressed in several types of cancers, especially colorectal cancer (CRC). Monoclonal antibodies (mAbs) are one of the fastest-growing sector of biopharmaceutical industry and have been widely used as a therapeutic agent for the treatment of cancers and autoimmune diseases. In this study, the two mAbs against extracellular domain of CLDN1, 3A2 and 6F6 (Fig. 1B and Fig. 1C, respectively) [1, 2], were theoretically investigated by molecular docking and molecular dynamics simulation in order to evaluate the antibodies-antigen binding behaviour. As a result, both mAbs preferentially bound to extracellular loop (ECL) 1 and extracellular loop (ECL) 2 of CLDN1. Docking results base on ZDOCK scoring function in ZDOCK, revealed that 6F6 exhibited the higher docking score than 3A2 toward CLDN1. From 100 ns MD simulations of 3A2/CLDN1 and 6F6/CLDN1 complex, 6F6/CLDN1 showed the lower binding free energy than 3A2/CLDN1 similar to the result of molecular docking. At the 6F6/CLDN1 interface, there are 4 key mAb residues, including P14, T87, S88 and V121 and 5 key residues of CLDN1, including Q343, M347, I350, R387 and F395. In summary, the *in silico* results suggested that 6F6 can serve as a candidate effective anti-CLDN1 monoclonal antibody to inhibit mCRC.

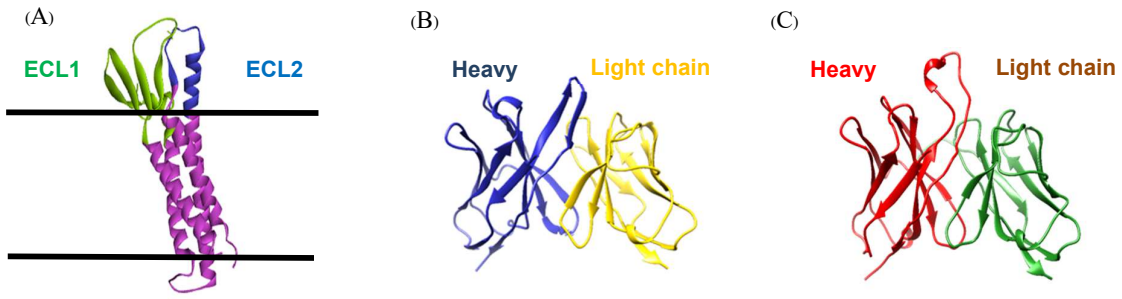

Figure 1. Structure of (A) claudin1, (B) 3A2 mAb and (C) 6F6 mAb

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BIO-O-06

Substrate binding mechanism of glycerophosphodiesterase towards organophosphate pesticides

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ABSTRACT

***Keywords**: Methyl parathion hydrolase, organo phosphate pesticides, MD simulations*

Methyl parathion hydrolase (MPH) is an enzyme from the metallo-β-lactamase superfamily, which hydrolyses a wide range of organophosphates. MPH has attracted recent attention as a promising enzymatic bioremediator. The crystal structure of MPH enzyme shows a dimeric form, and each subunit contains a binuclear metal ion center. MPH demonstrates metal-ion-dependent selectivity patterns. The origins of this remain unclear but are linked to open questions about the more general role of metal ions in functional evolution and divergence within enzyme super families. We aimed to investigate and compare the binding of different organophosphate pesticides. For this study MPH from *Ochrobactrum sp.* was obtained and molecular docking was performed with different classes of organo phosphate pesticides such as phosphomonoester (methyl paraxon, dichlorvos), thiophsphotriester (Diazinon, Chlorpyrifos), S substituted thiophsphotriester (Profenofos), phosphorothioester (Ethion, Malathion) using Cdocker. Refined pose obtained from molecular docking was chosen for classical MD simulations using AMBER16 for 100 ns. The distance between the two Zinc metal ions were found to be stably around 3.0-3.5 Å. D255 and a hydroxyl ion acted as bridging ligand and coordinated with both the metal ions. The alpha metal ion coordinated with D151, H152, D255 and H302. It was found to be more buried and did not coordinate with the pesticide. Instead, the less buried beta metal ion was found to be coordinated with some pesticides. It was seen that the coordination of beta metal ion was perturbed to accommodate the bulky pesticides. In addition, the inhibition of the MPH enzyme by few of the carbamate and pyrethroid pesticides was also studied to understand the synergism of the pesticides. Computational studies of pesticides as opposed to the natural substrate mimics provide a better understanding due to bigger size and the formal charges involved in the pesticide. The ability of the *in-silico* analysis presented here could be informative for increasing enzyme stability and activity.

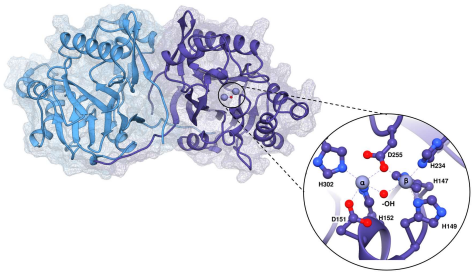

Figure 1. The 3D structure of homodimeric MPH, in which chain A and B are shaded by deep blue and light blue colors, respectively. The close-up regions for active site; Zn metal ions with its coordinating amino acids

BIO-O-07

Computational study on pyrazolopyran-based inhibitors against Plasmodium serine hydroxymethyltransferases

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ABSTRACT

***Keywords**: Serine hydroxymethyltransferase, Plasmodium falciparum, Plasmodium vivax, pyrazolopyrans, molecular dynamics, free energy calculation*

Serine hydroxymethyltransferase (SHMT), one of the ubiquitous enzymes involved in one-carbon metabolism, has been considered as a promising novel antimalarial drug target due to its main catalytic function in conversion of serine and tetrahydrofolate to glycine and 5,10-methylenetetrahydrofolate, a required substrate for the de novo synthesis of purine and pyrimidine nucleotide. In this study, structural insight into the recognition of two potent pyrazolopyran-based inhibitors (pyrazolopyran(+)-85 and pyrazolopyran(+)-86) [1] in *Plasmodium* SHMTs was studied by molecular dynamics simulations for 500 ns using AMBER16 program. The results revealed that all the *Plasmodium* SHMT–inhibitor complexes remained stable during the last 100 ns, as indicated by the low fluctuation of the root-mean-square deviation and the steady number of H-bonds along the simulation time. Based on the solvated interaction energies, pyrazolopyran(+)-86 showed the stronger binding affinity towards *Plasmodium* SHMTs than pyrazolopyran(+)-85 by ~2 kcal/mol. It was better stabilized by more H-bond formations with the SHMT binding pocket residues and a lower solvent accessibility to ligand binding. Therefore, pyrazolopyran(+)-86 could be used as the template for future design and development of new antimalarial drug.

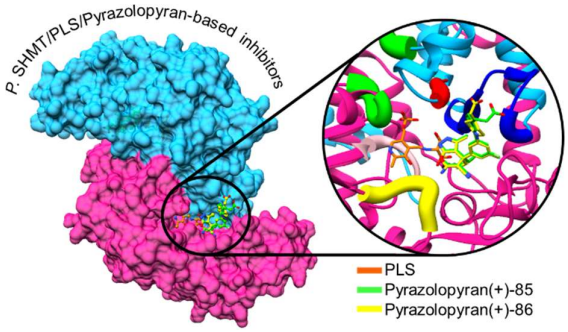

Figure 1. Overlay structure of pyrazolopyran-based inhibitors in *Plasmodium* SHMT.

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BIO-O-09
Theoretical simulations of Musashi RNA binding protein 1 in complex with target RNA

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ABSTRACT

***Keywords**: MSI1, RNA-binding proteins, ZIKV, MD simulation*

The Musashi (MSI) family of RNA-binding proteins, comprising the two homologs Musashi-1 (MSI1) and Musashi-2 (MSI2), typically regulate translation and are involved in cell proliferation and tumorgenesis. MSI also promotes the replication of Zika virus, has triggered further investigations of the biochemical principles behind MSI-RNA interactions. In this study, various of RNA were studied by use molecular dynamics simulation. The MD simulations were performed until 100 ns and calculated the binding free energy from Poisson-Boltzmann (MM/PBSA) and generalized Born surface area (MM/GBSA) together with solvated interaction energy (SIE) suggested that GUAGU display significantly greater binding affinities than those of the three RNA (GUUGU, GGAGU and GAUGU). Several protein residues (F23, W29, R61, F63, F65, F96, R98 and R99) were involved in binding to RNA through electrostatic attractions and H-bond formations. These findings provide an in-depth understanding the interaction between MSI1-RNA.

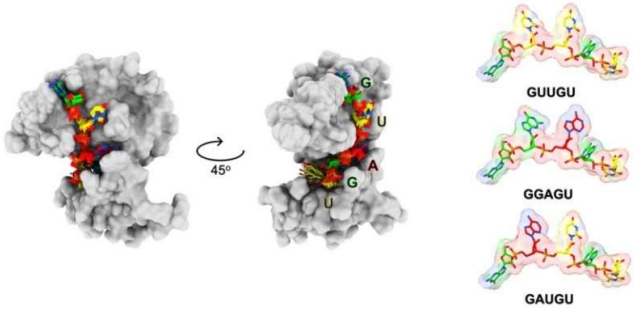

Figure 1 .The superimposition 20 model of Msi1-RBD1)PDB ID :2RS2 (and three additional pentamers GUUGU, GGAGU and GAUGU

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BIO-O-10
Drug evaluation of darunavir analogs on the mutated HIV-1 protease

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ABSTRACT

***Keywords**: Human immunodeficiency virus type-1 protease, Acquired immunodeficiency syndrome, Darunavir, HIV-1 protease inhibitors, Interaction energies*

Human immunodeficiency virus type-1 (HIV-1) protease is a successful target in the suppression of Acquired immunodeficiency syndrome (AIDS) progression by cleaving viral polyproteins contributing to mature structural and functional proteins [1]. Darunavir (DRV), approved by the Food and Drug Administration (FDA), is one of the potent HIV-1 protease inhibitors (PIs). DRV interacts with HIV-1 protease via both hydrophobic and hydrogen-bonding interactions within the active site. However, the mutations in HIV-1 protease were found to decrease DRV susceptibility [2]. In this study, we design and screen one hundred darunavir analogs in silico. The docking results showed that the top five analogs could interact with the HIV-1 protease at the active site significantly better than the darunavir. Then these analogs were investigated by 200-ns molecular dynamics simulations using the AMBER16 program. All results of the root-mean-square deviation, the steady number of H-bonds, and the binding free energies could be used to determine the potency and effectiveness of these analogs as candidates for developing PIs. The best suitable analog will be synthesized and tested with biological activity in further study.

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BIO-O-11

Molecular mechanism of unique interactions between APC gene and gold nanoparticles: *in silico* study for a universal cancer screening kit

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ABSTRACT

***Keywords**: Molecular dynamics (MD) simulations, DNA methylations, Gold nanoparticles (AuNPs), Colorimetric sensor,*

DNA methylation is a biological process by which methyl groups are added to the 5′ position of the pyrimidine ring of cytosines. The DNA methylation profile on a promoter region of adenomatous polyposis coli (APC) gene plays a critical role in the epigenetic change that may trigger the onset of various cancers. The detection of DNA methylation on the promoter of the APC gene has become a promising candidate for early cancer diagnosis. Colorimetric sensor based on the assembly of gold nanoparticles (AuNPs) demonstrates rapid sensing and low-cost approach which can be further developed as point-of-care diagnostic tools. To gain molecular-level insights into the signature interactions between methylated DNA and AuNPs, molecular dynamics (MD) simulation was used to investigate: (i) the conformation of methylated DNA in aqueous solution; (ii) the physicochemical property of methylated DNA; (iii) physisorption of methylated DNA in the stabilization of cysteamine-capped AuNPs (Cyst/AuNPs); (iv) mechanism of DNA methylation detection via assemblies of Cyst/AuNPs. Our simulations illustrated different conformation of DNA with different methylation profile in the aqueous solution. The methylated DNA shows higher aggregation once compared with the unmethylated DNA. In the presence of Cyst/AuNPs, large aggregation of methylated DNA can prevent AuNPs from the agglomeration due to the steric hindrance. The backbone of oligonucleotides played a remarkable role in the adsorption of the DNA onto the gold surface. The oxygen, nitrogen, and methyl group in methylated DNA demonstrated non-covalent interaction between DNA and gold surface. The elucidation of adsorption of methylated DNA onto the gold surface paves the way for a novel designing of colorimetric AuNP-based biosensor for DNA methylation detection and it can be utilized as universal cancer screening.

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BIO-O-12

Source of oseltamivir resistance due to single E276D, R292K, and double E276D/R292K mutations in H10N4 influenza neuraminidase

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ABSTRACT

Keywords: *Oseltamivir resistance; neuraminidase; E276D/R292K mutant; Molecular dynamics*

Influenza is a respiratory contagious disease infecting people all around the globe. The Center for Disease Control and Prevention had estimated that from 1 October 2018 to 4 May 2019, there have been about 40 million flu patients, in which about 50 thousand cases have died. Many subtypes of influenza have developed drug resistance due to high mutation rates. Neuraminidase (NA) is the glycoprotein on the virus particle surface. Its function is to cleave the glycosidic bond with the sialic acid, leading the new virus to be able to infect other uninfected cells. Therefore, it is a promising protein target for drug design and development. The E276D and R292K NA mutations in the H10N4 influenza virus have been reported to cause drug resistance. In this study, molecular dynamics simulations and free energy calculations were applied to study the source of oseltamivir resistance in E276D, R292K, and E276D/R292K NA strains. The obtained results suggested that all studied mutants reduced the number of contact atoms, interaction energies, H-bonds, per-residue interaction energies, and total binding free energies towards the oseltamivir binding, resulting in a lower susceptibility. Only the interactions at residues 118, 119, and 371 were maintained in stabilizing the oseltamivir. The opening at 150- and 430-loops in E276D and double mutations caused the drug unbinding from the active site, increasing water accessibility into the binding pocket of NA enzyme.

BIO-O-13
Computational Screening of Newly Designed Compound Against Coxsackievirus A16 and Enterovirus A71

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ABSTRACT

***Keywords**: Hand foot and mouth disease (HFMD), Coxsackievirus A16, Enterovirus A71, Rupintrivir*

Outbreaks of hand, foot, and mouth disease (HFMD) occur around the world. It is caused by the Coxsackievirus A16 (CV-A16) and Enterovirus A71 (EV-A71) that belong to the *Enterovirus* genus. Unfortunately, neither an anti-HFMD drug nor a vaccine is currently available. Rupintrivir, one of drug candidates for HFMD treatment, has been attactive for the development of its analogs with board biological activities. Rupintrivir is an inhibitor for 3C protease of CV-A16 and EV-A71, an enzyme that plays a crucial role in viral replication process. *A previous study suggested that* rupintrivir analogs containing hydroxymethyl group at the P2 site showed the higher binding affinitiy than rupintrivir. In the present study, we aimed to search for newly designed compounds from rupintrivir analogs toward 3C protease using the Molecular Mechanics Poisson-Boltzmann or Generalized Born Surface Area (MM/PB(GB)SA) and molecular dynamic (MD) simulation approaches. From MM/PB(GB)SA calculations, our results showed that among 20 designed rupintrivir analogs there were 5 compounds (P1'-1, P2-m3, P3-4, P4-5, and P4-19) which had lower binding free energy than rupintrivir. From MD simulation analysis, P2-m3 showed stable system during the simulation for 500 ns from the RMSD value. It showed the highest number of hydrogen bond, number of contact atoms and binding free enegy with 3Cpro CV-A16 and EV-A71 in the last 50-ns of the three-independent simulation. Therefore, this compound is likely to have the binding efficiency better than rupintrivir. However, druglikeness, ADMET properties, and biological testing need to be performed to ensure that this compound can serve as a more potent anti-HFMD agent.

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POSTER PRESENTATION

BIO-P-01

Free Energy Calculations of Melatonin Permeation through Niosome Bilayers: A Molecular Dynamics Study

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ABSTRACT

***Keywords**: Melatonin, Cholesterol, Span60, Potential of mean force*

Molecular permeation through lipid membranes is a fundamental biological process that is important for small neutral molecules and drug molecules. Niosomes are vesicular systems comprising of bilayer made up of non-ionic surfactants such as Span60 (sorbitan monostearate) with cholesterol inclusion. They have been promoted as an excellent carrier for encapsulating both hydrophilic and lipophilic drugs. In this work, we have investigated the permeation of melatonin drug through niosome bilayers using molecular dynamics simulation. The permeation of melatonin through niosome bilayers with the addition of 0, 25, and 50 mol% cholesterol has been investigated by using the free energy calculations via the potential of mean force (PMF) method. The umbrella sampling technique was employed to the PMF calculations. The results showed that the free energy barrier of niosome bilayers decreased with cholesterol addition. The free energy barrier of the niosome bilayer with 50 mol% cholesterol is lower than the others, suggesting that the translocation of melatonin through the membrane is faster. Additionally, it can be observed that melatonin preferred to locate at the hydrophilic region (the head group of Span60). Therefore, the niosome bilayer with 50 mol% cholesterol inclusion exhibited the highest permeability, leading to easier translocation of melatonin through the membrane. The addition of cholesterols into the niosome bilayers significantly influences not only the permeability of melatonin molecule but also the bilayer structure.

Table 1. The free energy profiles of melatonin calculated by potential of mean force with 0, 25, and 50 mol% cholesterol.

Model	position of minimum (nm)	ΔG_{water} (kJ/mol)	ΔG_{pen} (kJ/mol)
spa_chol(0:0)	3.00	19.56	143.65
spa_chol(75:25)	2.91	25.84	91.52
spa_chol(50:50)	2.21	37.44	49.02

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BIO-P-02

Computational study of N501Y mutation in receptor binding domain of SARS-CoV-2 spike protein binding to human angiotensin-converting enzyme 2 receptor

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ABSTRACT

***Keywords**: SARS-CoV-2; N501Y mutation, S protein RBD, ACE2, MD simulation*

The recent N501Y mutation in the receptor binding domains (RBD) of SARS-CoV-2 spike protein has been reported to increase its binding efficiency to the human angiotensin-converting enzyme 2 (ACE2) receptor. Clearly, the spread of N501Y SARS-CoV-2 has increased dramatically and continuously compared to WT. The RBD binding with ACE2 (figure 1) is the one of important key of increasing new spread of SARS-CoV-2 [1]. In this study, the molecular structural and energetic properties of wild-type (WT) and N501Y SARS-CoV-2 complexed with ACE2 were studied using molecular dynamics (MD) simulations and binding free energy based on solvated interaction energy (SIE) method. The obtained results revealed that the binding affinity toward ACE 2of N501Y RBD was higher than that of WT RBD, consistent well with the lower water accessibility at the protein–protein interface and the higher compactness of N501Y RBD/ACE 2complex, driven by a formation of π-π interaction (Y-501Y(41. In addition, the increased susceptibility of hot-spot residues of N501Y RBD was promoted by the formation of H-bonds and contacting atoms. Altogether, the N501Y enhances affinity of the prefusion state on the membrane during the fusion machinery in human. The obtained results could be helpful for the design of novel vaccines.

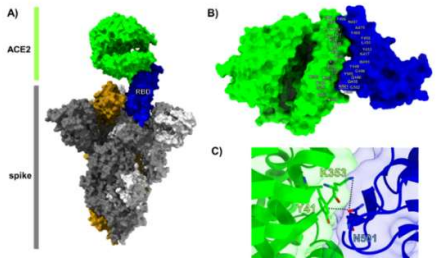

Figure 1. (A) Crystal structure of SARS-CoV-2 RBD (blue, open form) bound to the ACE2 (green) receptor (PDB ID 7A94). B) RBD binding with ACE2 complex. (C) interaction between N501 residue of RBD and K353 and Y41 residues of ACE2.

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BIO-P-03
In silico and *in vitro* studies on inclusion complexation of anthraquinone derivatives with β-cyclodextrin derivatives

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ABSTRACT

***Keywords**: β-cyclodextrin; inclusion complex; anthraquinones; emodin; molecular dynamics simulation; cytotoxicity; lung cancer.*

An enormous amount of research, ranging from co-solvency to nano-crystallization [1], has been carried out to enhance the water solubility of poorly soluble drugs. Out of ample techniques, complexation with β-cyclodextrin (βCD) has gained a lot of research attention due to its unique structure where many kinds of lipophilic guest molecules are entrapped into its hydrophobic cavity [2]. Anthraquinones, an important class of organic compounds prevalent in nature, have been employed as natural dyes, laxatives, and herbalism historically to chemotherapeutic agents nowadays. In this study, we investigated the cytotoxicity of 6 anthraquinones (Ventilanone K, Emodin, Chrysophanol, Aurantio-Obtusin, 1-O-methyl-2-methyoxychrysophanol, and Questin) toward A549 human lung cancer cell line. Notably, Emodin (6-methyl-1,3,8-trihydroxyanthraquinone) exerted the most potent cytotoxic effect with IC_{50} value of 34.27 ± 1.27 μM. The anti-cancer activities of Emodin via DNA intercalation, cell cycle arrest and apoptosis [3] have been well reported. However, its usage in pharmaceutical applications has been restricted due to its poor aqueous solubility. To address this issue, we performed a series of complexation of Emodin with βCD and its derivatives: 2-hydroxypropyl-β-cyclodextrin (HP-βCD), and 2,6-di-O-methyl-β-cyclodextrin (DM-βCD), to identify the most promising drug carrier with regards to water solubility enhancement and augmented biological properties through host-guest complexation by *in silico* study: molecular docking, all-atom molecular dynamics (MD) simulations and binding free energy calculations via molecular mechanics/Poisson-Boltzmann (generalized Born) surface area (MM/PB(GB)SA) and *in vitro* study: cytotoxicity (MTT) assay, and phase solubility analysis. Our findings suggest that HPβCD could be utilized as the most feasible host molecule for Emodin, with $\Delta G_{bind,\ MM/GBSA}$ value of -4.13 ± 4.27 kcal/mol and 1:1 host-guest stoichiometry with stability constant (Ks) value of 1681 ± 2.74 M^{-1} at 37°C, respectively.

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BIO-P-04
Computational screening of next-generation Epidermal growth factor receptor tyrosine kinase inhibitors

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ABSTRACT

Keywords: *furopyridines, EGFR-TK, molecular docking, molecular dynamics simulation, anticancer drug screening*

Epidermal Growth Factor Receptor (EGFR) is one of four transmembrane proteins that plays an important role in cellular signaling pathways [1]. EGFR mutations have been linked specifically to non-small cell lung cancer [2]. EGFR kinase inhibitors are classified into several generations such as osimertinib, which is the third generation inhibitor [3]. This drug indicated potent activity against mutant forms and nominal activity with wild-type EGFR (EGFR-WT) [4]. After long-term clinical treatment with osimertinib, 40% of patients developed to T790M/L858R/C797S mutation (EGFR-TM). Therefore, the screening for new potent compounds against both EGFR-WT and EGFR-TM is necessary. In this study, the furopyridine compounds were elucidated using molecular docking, molecular dynamics simulations and free energy calculation based on the solvated interaction energy (SIE) method. The obtained results revealed that the seven screened furopyridine compounds showed binding ability with both EGFR-WT and EGFR-TM better than osimertinib. From SIE method, compound PD13 shows the highest binding affinity with ΔG_{bind} value of −11.81 ± 0.03 kcal/mol and -9.70±0.02 kcal/mol for EGFR-WT and EGFR-TM, respectively, which is greater than osimertinib (-8.51±0.03 kcal/mol). The obtained information suggests that compound PD13 could be served as a new candidate for further developing an anti-cancer drug.

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BIO-P-05

Temperature effect on the structure and dynamics of melatonin inside niosome bilayers: A molecular dynamics approach

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ABSTRACT

***Keywords**: Melatonin; Niosomes; Entrapment; Coarse-grained, Drug Delivery*

The structural properties and dynamics of melatonin inserted into niosome bilayers have been studied by using coarse-grained molecular dynamic simulations. The simulations with temperatures varying from 27°C to 67 °C have been carried out to investigate on temperature dependence of the bilayer structure and melatonin entrapment. The simulation results revealed that the area per lipid increased while the bilayer thickness decreased with temperature increasing. Furthermore, more melatonin molecules trended to move into the bulk water at the high temperature. However, they remained inside into the bilayer at the moderate temperatures. Cholesterol additive plays a major role in the entrapment of melatonin that inserted into the niosome bilayer. Increasing the temperature caused the phase transition of niosome bilayer from the gel to liquid-ordered phases. At the lower temperature the niosome bilayer with melatonin inclusion was in the gel phase while the higher temperature it was in the liquid-ordered phase.

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BIO-P-06
Lomitapide, a Lipid-Lowering Agent May Have Clinical Significance Towards the Cure of P38α MAPK-Related Diseases

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ABSTRACT

Keywords: *MAPK, P38α-MAPK, Drug Repositioning, Molecular Docking, In silico screening*

P38α mitogen-activated protein kinase (p38α MAPK), one of the p38 MAPK isoforms participating in a signalling cascade, has been identified its pivotal role with the regulation upon great deals of physiological processes such as cell proliferation, differentiation, survival and death [1]. With biological proven evidences, enormous efforts have been collectively putting onto searching effective drugs for the reason that it could be a promising strategy for the management of cancer, neurodegeneration, and inflammatory diseases. Here, with shedding light on the advancement of computational biology contributed to the pre-clinical stage of drug discovery and development, we found that Lomitapide approved to use as pharmacological therapy in patients with homozygous familial hypercholesterolemia (HoFH) [2] could be able to act as a potent inhibitor targeting p38α MAPK. *In silico* results revealed that Lomitapide has greater binding patterns and characteristics when compared to BIRB796 (a well-known p38α MAPK inhibitor). Binding energy predicted from both molecular docking and solvated interaction energy (SIE) approaches exhibited a significant lower value than BIRB796 indicating an enormous greater binding capability towards the binding-site cleft. Specifically, we found that Van der Waals interaction energy was the main force driven the formation of the enzyme-drug-like complex. In addition, some other parameters were found to be corresponding with the higher magnitude of Lomitapide binding recognition. For instance, non-covalent contacts of any atoms counted within the 5.0 Å sphere of the ligand were quantitatively higher, which tends to have greater intermolecular interactions whereas the surface area occupied by water molecules termed SASA showed a gradual lower value compared to a reference complex. Thus, for the lines of evidence regarding the computational results, Lomitapide could become a viable candidate for further investigation necessary for guiding its clinical significance towards the therapeutic potentials of p38α MAPK-related diseases.

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