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Adriana Rathner et al., Biochem Mol biol J, Volume 4
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STUDY OF EXTRINSIC PSB PROTEINS OF PHOTOSYSTEM II BY SOLUTION NUCLEAR MAGNETIC RESONANCE

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Nuclear magnetic resonance (NMR) is a powerful technique which enables characterization of various biomolecules in solution. This way one is able to track more accurately the dynamic properties and changes in the structure over time and varying conditions (temperature, salt concentration, ligand addition, and pH). Psb proteins of photosystem II are a class of extrinsic proteins located on the cytosolic part of the oxygen evolving center. They help to maintain proper conditions for the water splitting reaction ultimately leading to the release of molecular oxygen. We have studied so far three representatives: PsbP (23 kDa), PsbQ (16 kDa) and PsbO (33 kDa). Using NMR we have been able to determine 3D structures of PsbP and PsbQ in solution including their highly flexible regions whose characterization was hindered with the use of other techniques (X-ray and Cryo-electron microscopy). The most interesting information about detailed interplay of those proteins and its dependence on the presence of metal cations has been studied using combination of techniques, such as titration and chemical exchange NMR technique (CEST), isothermal titration calorimetry (ITC) and microscale thermophoresis (MST).

Biography

Adriana Rathner obtained her Double Bachelor's Degree in Biological Chemistry at Johannes Kepler University Linz (Austria) and the University of South Bohemia (Czech Republic) in 2010. Her Bachelor's thesis dealt with the optimization of synthesis of dipeptides for isotope labeling and pilot expression of outer surface protein from pathogenic Borrelia, respectively. She then continued in the Joint Master's Program of Biological Chemistry and within her thesis, worked with recombinant photosynthetic protein PsbP and its initial NMR characterization in the group of Professor Norbert Müller (JKU Linz). Since 2013, she is a PhD student in the same group with the main focus on large scale production of isotopically labeled proteins of photosystem II and their subsequent study by various solution nuclear magnetic resonance (NMR) techniques.

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CHARACTERIZATION OF PROTEIN-EXCIPIENT INTERACTIONS FOR DESIGNING FORMULATION

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Proteins often perform a diverse and complex set of functions within the cell, including catalyzing metabolic reactions, transport of specific substances from one location to another, etc. Therefore, proteins, also called biologics, are regularly used in protein-based therapies to treat diseases. A major potentiality of biologics resides in their intrinsic compatibility with living systems, in comparison with small molecule drugs. Biologics are often characterized by high specificity and potency with low toxicity and thus have interested many pharmaceutical industries. Several challenges confront pharmaceutical scientists involved in the development of protein therapeutics. For instance, the proper stabilization of biologics is one of the major concerns. To overcome this issue, excipients play a major role in stabilizing biologics to prevent protein-protein interactions and hence aggregation. Currently, a detailed molecular understanding of the effect of different physicochemical formulation conditions on the stability of proteins is sparse, as molecular interactions are difficult to investigate experimentally at the molecular level. Thus, computational approaches, as applied in the current study, can provide insight on the single-molecule level. This rational approach is an attempt to understand the combined effect of pH and salinity on the protein stability. We investigated the effect of pH and ionic strength on the wild-type plectasin, and the three variants (PPI41, PPI42, PPI43). Furthermore, independent protein thermodynamic integration MD simulations were performed to understand conformational stability due to the presence of cysteines bonds. These results are further supported by NMR and fluorescence studies. Additionally, studies have been performed to identify potential hotspots for excipient-protein interactions using free energy approaches such as implicit solvent molecular mechanics (MM-PBSA) and explicit solvent linear interaction energy (LIE) methods, relative binding affinities of excipients to the proteins are predicted in order to rank excipients and to determine the effect of excipients on protein dynamics and flexibility. These results will be further supported by NMR studies.

Biography

Sowmya Indrakumar holds a Bachelor of Science (by Research) and Master of Science degree in Biology from Indian Institute of Science, Bangalore, India. Throughout her undergraduate studies, she was a recipient of 'Innovation in Science Pursuit for Inspired Research-Department of Science & Technology (INSPIRE-DST) fellowship. In 2016, she became part of the PIP-PI (http://www.pippi.kemi.dtu.dk/) project as a Ph.D. researcher at Technical University of Denmark, Denmark. This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant.

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STORMORKEN SYNDROME DISEASE STIM1 PROTEIN STUDIED BY HIGH RESOLUTION NMR

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STIM1 serves as calcium sensor protein in the endoplasmic reticulum of the cell which extends into the cytosol and oligomerises upon calcium store depletion. The cytosolic part of STIM1 consists of one long and two short coiled coil domains directly involved in homo-oligomerization leading to spatial elongation of the STIM1 protein and activation of the Orai calcium channel. The Stormorken syndrome associated with a single point mutation (R304W) within this region of STIM1 results in permanent activation of Orai channel. Using high resolution solution state NMR we have found a helix elongation within the short coiled coil domain of the mutant close to the mutation position with respect to the wild type STIM1. These findings corroborate the increased propensity of this domain to form homomers destabilizing the resting state of STIM1, which leads to the increased channel activation.

Biography

Petr Rathner has completed his Double Degree Mgr/MSc in 2013 from Johannes Kepler University of Linz (Austria) and University of South Bohemia (Czech Republic). Currently, he is a PhD student in the group of Professor Norbert Müller Nanocell research (JKU Linz, Austria) focusing on biomolecular nuclear magnetic resonance spectroscopy.

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MAPPING THE ACTIVE SITE OF EPSILON-TRIMETHYLLYSINE HYDROXYLASE

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ε-trimethyllysine hydroxylase (TMLH) is a non-heme Fe(II) and 2-oxoglutarate (2OG) dependent dioxygenase located in the submitochondrial matrix. This enzyme is crucial for the stereospecific oxidation of ε-trimethyllysine (TML) to β-hydroxytrimethyllysine (HTML), the first step in the biosynthesis of L-carnitine. It is proposed that the regulation of enzymatic activity of TMLH may have more potent cardioprotective effect than meldonium (clinically used anti-ischemia drug) that is an inhibitor of γ-butyrobetaine hydroxylase (GBBH), the final step of the L-carnitine production. Due to failure of the crystallographic methods there is still lack of information about the structure of the TMLH and especially about its active site. In this work, we applied *in silico* and *in vitro* methods to design the possible active site of TMLH. The structure of the TMLH was modeled using homology modeling approach based on the closest homolog, GBBH (used as template). However, the overall similarity between both enzymes was slightly below 30%. Thus, various modeling softwares were tested, and the resulting structures were optimized during molecular dynamics simulations. This approach gave the insights into possible enzyme fold. Next, the NMR protein-ligand binding experiments (T1ρ, waterLOGSY and ST1D) and the enzymatic assay (reaction monitored by 1D ^{1}H-NMR) revealed some crucial structure-activity relationships (SAR) that in combination with molecular docking and previous *in silico* data allowed to construct estimated active site of TMLH.

Biography

Zelencova D is a PhD student at the Riga Technical University, Latvia. She is the Research Assistant at the Latvian Institute of Organic Synthesis: NMR group.

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Kenneth Lee et al., Biochem Mol biol J, Volume 4
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INVESTIGATING THE ROLE OF NS2B DYNAMICS IN DENGUE VIRUS NS3 PROTEASE FUNCTION

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The proteins of the dengue virus are expressed as a single polyprotein, which is then processed proteolytically into individual functional fragments by proteases from both the host and the virus itself. The viral protease is the N-terminal domain of the non-structural protein 3 (NS3pro) and is an attractive target for drug-based therapeutic intervention. NS3pro by itself is expressed in the inclusion bodies and requires a 47-residue hydrophilic region of the non-structural protein 2B (NS2B) for its correct folding and enzymatic activity. As NS2B is flexible and dynamic, existing crystal structures are unable to give a complete picture of the NS2B-NS3pro complex for drug development. A method inspired by a recent paper was used for the partial isotopic labelling of the NS2B-NS3pro complex, which simplifies the multidimensional spectra obtained through nuclear magnetic resonance (NMR) experiments. We aim to find out how the dynamics of NS2B contributes towards the proteolytic activity of the dengue virus NS3pro, through various NMR dynamics experiments. Relaxation dispersion data reveal that the C-terminal portion of NS2B unfolds itself around 4% of the time. Mutants of NS2B were generated to explore how both the dynamics and protease activity change with the mutations.

Biography

Kenneth Lee is currently doing his PhD in the Department of Biological Sciences, of the National University of Singapore. He is expecting to complete his PhD in 2018.

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Wei Liu et al., Biochem Mol biol J, Volume 4
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MPGA: A MIXED ALGORITHM OF MATCHING PURSUIT AND GENETIC ALGORITHM FOR STRUCTURE CHARACTERIZATION OF LARGE INTRINSICALLY DISORDERED PROTEINS

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Structure characterization of intrinsically disordered proteins (IDPs) remains a key obstacle in understanding their functional mechanism. Due to the highly dynamic feature of IDPs, structure ensembles instead of static unique structures are often derived from experimental data. Several state-of-art computational methods have been developed to select an optimal ensemble from a pre-generated structure pool. For a large IDP, we usually need a large structure pool to sample the possible conformational space and a big structure ensemble to describe its dynamic feature. In such a case, the search space becomes too big to be adequately explored by conventional algorithms, causing the decline of their optimization performance. We developed a matching pursuit genetic algorithm (MPGA), which takes advantages both from matching pursuit (MP) to reduce the search space and from genetic algorithm (GA) to free the requirement on the constraint types for structure determination. The MPGA method was tested in a structure ensemble selection from a large pool (>200 k) of an IDP with 306 amino acids. By comparing with conventional GA, MPGA demonstrated both higher calculation speed and better optimization result.

Biography

Wei Liu has completed his PhD from Nanyang Technology University, Singapore. He is a research fellow of National University of Singapore, Singapore .

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Yamina C, Biochem Mol biol J, Volume 4
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ANTIMACROBIAL ACTIVITY AND SYNTHESE OF THIOSEMICARBAZIDE AMINO ACID DERIVES

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The 5-(1,5diamino-pentyl)-1-amino-1H-1,3,4-triazole-2-thiol [1] and the 5-(1,5 diamino-pentyl)-4-amino-S-glucosyl-1,2,4-triazole [2] derivatives form amino acid were synthesized. The synthetic intermediates, ester, hydrazid and and thiosemicarbazide derivates have show a significant tendency to form S-Nucleosides with sugar (glucose). A novel nucleoside from oxadiazol the derivative with glucose was synthesized and was detected by IR spectroscopy and NMR [3]. The antimicrobial activity for final and synthetic intermediates *in vitro* against the microorganisms: *Echerichia coli, Pseudomonas aeruginosa, Staphylococus aureus* and *Salmonelle chiguer* were examined and some products showed noticeable activity against the tested miroorganisms [4].

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Biography

Yamina C has completed her PhD at the age of 32 years from Oran University, ALGERIA. She is the student of Mostaganem University, Algeria. She has one publication on journal of European Chemical Bulletin "Synthesis and Antimacrobial Activity of Some New L-Lysine Glycoside Derivatives".

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F. Ouazani et al., Biochem Mol biol J, Volume 4
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BIOSORPTION OF ETL DYE BY ARUNDO-DONAX SORBENT: BOX-BEHNKEN OPTIMIZATION, EQUILIBRIUM AND KINETIC STUDIES

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This research study is divided into two parts; the first part investigates the batch ETL dye sorption by Arundo-donax. The sorbent was synthesized and characterized by scanning electron microscope (SEM) and Fourier transform infrared spectroscopy (FTIR). The effects of pH, initial dye concentration, contact time and mass sorbent in the efficiency of ETL sorption were investigated. Furthermore, pseudo-first and second-order kinetic models were also used to analyze sorption kinetics. The equilibrium adsorption results were fitted by the Langmuir and Freundlich isotherms. Maximum amount ETL removal 56.49 mg/g was observed at pH 2, sorbent weight 50mg and contact time 60min.

In the second part the aim was to evaluate the impact of operating conditions in the efficiency of Arundo-donax to remove ETL dye. From the first part, three factors were chosen (initial solution concentration of ETL, pH solution and Arundo-donax weight). These factors were investigated using three level box behnken design to optimize operating conditions. Analysis of variance (ANOVA) were using to testing the obtained linear model. The pH solution and initial dye concentration have an important effect compared to the effects of others factors. Correlation coefficient R^2 was found 0.99, which mean the accordance between the model and the experiment data.

Biography

Ouazani F is PhD student in Laboratory of materials recovery in Mostaganem University, Algeria. She continues her works on water treatment using physicochemical protocols. She has 2 publications.

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EXPERIMENTAL INOCULATION IN PREGNANT SOWS WITH BOVINE VIRAL DIARRHEA VIRUS 2

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Bovine viral diarrhea virus (BVDV) is genetically and serologically related to other members of the genus Pestivirus, such as classical swine fever virus, and may cause reproductive problems, but there is still a lack of research to determine the pathogenicity in different gestational periods of sows (pigs) and consequences in newborn piglets. The objective of this work was the analysis of the effect of bovine viral diarrhea virus infection in gestation and in swine neonates. Twelve pregnant sows divided into five groups were used, which were inoculated experimentally with the BVDV-2 strain, one group with 30 days before insemination (G0); three groups during gestation, first (G1), second (G2) and last third (G3); and the fifth control group (G4). Samples of blood, serum and nasal swabs were collected every three days from the day of inoculation through the farrowing. On the day of delivery, half of the newborns were euthanized to obtain blood and organ samples at necropsy. The collected samples were analyzed by means of the virus neutralization, real time RT-PCR, blood count and histopathology. The RT-qPCR was performed using the TaqMan system, Thermofisher™-VetMAX™-Gold BVDV Detection Kit commercial kit. Serial dilutions of VS253 were diluted at 100 and 107 to detect the limit of RT-qPCR. All sows seroconverted during the gestational period, except the control group and BVDV-2 was detected in blood and nasal swabs in G0, G1, G2 and G3 sows with a Ct<36, the viremia was detected from day 3 post-infection (dpi) through 12 dpi and viral shedding was detected from 6 dpi through 23 dpi, and the piglets developed gliosis. G1 sows presented thrombocytopenia at day 36 after inoculation. The dynamics of BVDV-2 infection in pigs was clarified, such as the serological and viremic profile, shedding phase and clinical characteristics; however, transplacental virus transmission was not detected.

Biography

Pereira D A is pursuing her PhD at the University of São Paulo, Brazil. Her expertise is in the health of swine. She works on laboratory techniques such as molecular and immunodiagnostics for swine diseases, especially RNA and virus (Pestivirus). She graduated in Veterinary Medicine in 2009. She received a scholarship from FAPESP (Brazilian Founding: process: 2015/08531-0) and has over 9 publications. She has also been serving as a member of Suinesp (Group of studies in swines).

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Christina Sungrapova, Biochem Mol biol J, Volume 4
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THE ROLE OF POLYAMINES AS THE ONCOMARKERS IN THE BLOOD

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The content of polyamines in the blood is of interest not only to researchers but also to practicing physicians. The levels of polyamines in the blood were examined as nonspecific cancer markers. However, like most other putative biochemical markers, they did not go into clinical practice because there was no simple, commercially available, low-cost, effective method for determining these compounds in the blood. Most of the methods currently used for the analysis of polyamines have different sensitivity and accuracy, require expensive and complex equipment.

Biography

Christina Sungrapova is graduate student of the Department of Biochemistry of the Medical Institute, RUDN University.

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HPLC SEPARATION OF ENANTIOMERS OF SOME ANTIFUNGALS USING COVALENTLY IMMOBILIZED POLYSACCHARIDE-BASED CHIRAL SELECTORS AND POLAR ORGANIC MOBILE PHASES

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Chiral antifungals are used as veterinary and human drugs, as well as agrochemicals. They are especially used to cure fungal infections that commonly occur on the nails, hair and skin. Those antifungals in use which show efficacy against fungal diseases are mostly target specific components of fungal plasma membrane or its biosynthetic pathways. Enantioselectivity of chiral imidazole and triazole derivatives in biological action, metabolism and pharmacokinetics is well documented. In this work, separation of enantiomers of some chiral antifungals was studied on two polysaccharide-based chiral columns by high performance liquid chromatography (HPLC) using polar organic mobile phases such as methanol, acetonitrile, ethanol and isopropanol. 10 chiral antifungal pharmaceuticals (ketoconazole, sertaconazole, miconazole, terconazole, tioconazole, isoconazole, fluconazole, luliconazole, posaconazole and itraconazole) were separated by Lux i-Cellulose 5 (cellulose 3,5-dichlorophenylcarbamate) and one experimental amylose based chiral column (amylose 3,5-dimethylphenylcarbamate) with the dimension 4.6x250 mm. The mobile phase flow rate was 1 mL/min and the temperature of the columns was kept at 25°C. Polar organic mobile phases offer certain advantages for separation of enantiomers such as short analysis time, high plate numbers and favorable signal to noise ratio. Used chiral columns offer good stability in pure polar organic solvents as well as wider variety of mobile phases. Finally, this study demonstrated the chiral columns based on cellulose 3,5-dichlorophenylcarbamate and amylose 3, 5-dimethylphenylcarbamate covalently attached to the surface of silica particles can effectively separate the chiral imidazole and triazole derivatives by using polar organic mobile phases.

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INFLUENCE OF THE OXIDATIVE STRESS ON THE SECRETION OF THE ENDOGENOUS ANTIMICROBIAL PEPTIDES IN HEREDITARY BLOOD DISEASES

Azizova G I, Dadasheva A R and **Efendiyev A M**
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Among the diseases of the blood, thalassemia occupies a special place, associated with a reduction or complete absence of synthesis of globin chains of hemoglobin. Azerbaijan is considered as an endemic zone of these inherited blood diseases, which makes conducted researches relevant. The aim of this work was to study the relationship between the thiol status of blood and the secretion of endogenous antimicrobial peptides. The blood of 57 patients aged 6-17 years was studied. All patients depending on the pathology were divided into the following groups: group I-20 children with a homozygous form of β-thalassemia, group II-37 children with G6PD deficiency. To assess the degree of oxidative stress of the body, carbonylated proteins (CP) and thiol status (TS) of blood were chosen as markers. To assess the level of secretion of endogenous antimicrobial peptides, a quantitative analysis of defensin and endotoxin in blood plasma was performed using the ELISA method. The research was carried out with the financial support of the Science Development Foundation of Azerbaijan. As a result of research, it was revealed that in group I patients, the amount of CP increased by 11%, in the group II patients CP increased by 1.6% and TS decreased by 1.5%. The level of defensin in group I increased by 2%, and endotoxin by 1.7%. In group II, these indicators increased by 1.7% and 2.3%, respectively. With the change of the body's TS, the secretion of α-defensin was increasing. In β-thalassemia, carbonylated proteins increase in the blood, thiol status decreases, which indicates at the increase of the influence of oxidative stress associated with frequent infectious complications and activation of neutrophils.

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SYNTHETIC BIOLOGY MEETS STRUCTURAL BIOLOGY: FROM PROTEIN COMPLEX STRUCTURES TO SYNTHETIC VIRAL NANOSYSTEMS

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Synthetic biology is the engineering of biology which enables a rational, bottom-up approach to design and construct artificial biological systems as well as the redesign of existing natural biological systems. Structural biology is the elucidation of molecular mechanisms of natural and artificial biological architectures, ideally at atomic resolution. Structural biology has drawn immense benefit from engineering and design, notably for the recombinant synthesis of biological specimens as objects of study. Recombinant technology relies on the delivery of customized, active biological circuits comprising of functionally arranged synthetic genetic material and regulatory elements into a variety of natural and engineered host organisms as the chassis. Synthetic biology approaches hold enormous promise to decisively advance structural biology in academic and industrial research and development programs, by accelerating all steps of circuit design, assembly and delivery, and enhancing available chassis by targeted engineering. Recent developments, their applications and potential for investigating the structure and function of complex multiprotein assemblies will be discussed.

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COMPUTER SIMULATION OF COLONIC PROPULSIVE ACTIVITY

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The primary functions of the large intestine (colon) are to store, process and expel fecal mass residues. These require sustained motor activity in the organ which is used for the generation of migrating myoelectrical complexes (MMC) in order to mix and propel the content. The aim of this research is to find an effective way to treat patients with constipation or diarrhea. The mathematical model of a segment of the gut with an enclosed bolus was constructed. The colon was represented as a thin deformable soft biological shell with the bolus modeled as a non-deformable solid sphere. The bolus in motion was subjected to dry and viscous friction, and the inertia forces were neglected. The results of simulations of movement patterns resembled those recorded experimentally and provided quantitative insights into the spatio-temporal patterns of changes in configuration, the distribution of contact forces over the bolus, and predicted the average velocity of colonic transit. Thus, a reciprocal relationship in the contraction of the longitudinal and circular smooth muscle was necessary to guarantee the "mixing" type of movements. Strong conjoint contractions of both muscle layers were necessary to expel the bolus from the gut. The dynamics of stress-strain distribution, demonstrated the rise in the intensity of active propulsive forces in the circular smooth muscle layer throughout the entire phase of propulsion of the bolus. Viscous, compared to dry friction had a marked effect on the average velocity of colon transit. Thus, the addition of osmotic (lactulose, sorbitol) and rapidly acting lubricant (mineral oil) laxatives, intraluminally shortened the time required for expulsion of the bolus significantly. The mathematical model of a segment of the gut reproduces qualitatively and quantitatively the dynamics of colonic transit. Viscous and not dry friction is the dominating parameter in the stability of propulsion.

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COMPUTER SIMULATION OF MULTIPLE NEUROTRANSMISSION IN THE HUMAN GASTRIC ANTRUM

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The aim of the study is to analyze *in silico,* the conjoint action of acetylcholine (ACh), nitric oxide (NO) and high concentrations of motilin (Mot) on myoelectrical activity of the gastric antrum under complex physiological stimuli. Acting alone at increasing doses, Mot steadily depolarizes smooth muscle, reduces the amplitude and shortens the duration of slow waves. These changes correspond to a significant rise in the basal muscle tone and the active force, T^a=16.1 mN/cm. The mechanical stretching of the antrum at a high frequency and the subsequent release of Ach, results in the production of regular high amplitude spikes on the crests of slow waves. Smooth muscle responds with strong phasic contractions, T^a =8.3 mN/cm. The application of Mot at 50-100 nM does not affect the cholinergically mediated myoelectrical activity, although it evokes contractions of inconsistent amplitudes: T^a=2.9-8.3 (mN/cm). The release of a "puff" of NO to the gastric antrum which has been exposed to ACh and Mot, fails to exert any inhibitory effect. When the addition of NO precedes ACh and Mot, acute short-lasting relaxations with min T^a =7.7 mN/cm are observed. The asynchrony between the firing rate of interstitial cells of Cajal and the presence of Mot at 85 nM causes the production of active forces of wavering strength. The antrum fails to relax completely. A lower frequency of ganglionic activity allows a greater degree of relaxation, T^a=8 mN/cm, and contractions of larger amplitude, 9.9 mN/cm. The results have unveiled intricacies of co-transmission by multiple neurotransmitters in the antrum of the human stomach and the dynamics of active forces development. The chronotropic allosteric interaction among ACh, NO, Mot and interstitial cells of Cajal plays a pivotal role in coordinated motor activity of the organ. Abnormalities in their interplay could lead to motor dysfunction.

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BIOINFORMATIC ANALYSIS OF GENE EXPRESSION PROFILES OF CRC SAMPLES BY RNA-SEQ DATA SET

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Introduction: MicroRNAs (miRNAs) are small non-coding RNAs, approximately 22 nucleotides in length that mediate translational repression of target messenger RNA (mRNA) transcripts. MiRNAs play a key role in cellular differentiation and proliferation, regulation of cellular metabolism, and are involved in the initiation and progression of cancer. Therefore, comparing of two states can illustrate which genes cause the cancer initiation and progression. RNA-seq is the best high throughput way to study the expression level of genes and microRNAs entirely in cells with different states. Some genes are overexpressed and some of them are down-regulated in different physiological conditions or diseases especially in cancer. The main purpose of the current study is to figure out the specific miRNAs between all the microRNAs and analyze their target genes to find out the connection between the dysregulator miRNAs and CRC-related pathways.

Materials & Methods: In this study, the microRNA expression level of 1061 malignant colorectal cancer and 30 normal samples were compared using TCGA database and python programing language. Fold changes were calculated for high-grade samples related to normal ones. From total 1882 microRNAs, 10 top differentially-expressed miRNAs that had significant p values ($p<0.05$) were chosen for further analyses. Then 3000 in-common target genes, by using microRNA, miRwalk and miRmap online tools, were selected. After that Mirfocus and Diana online tools were intended to analyze miRNA-target gene pathways and the related miRNA annotations. Finally, KEGG database and Panther online tool were used to illustrate which signaling pathways are important in colorectal cancer based on microRNA function.

Results & Conclusion: Analysis of top differentially expressed microRNAs including hsa-miR-9-3, 9-1, 9-2, 200a, 1307, 191, 210, 192, 17, 1511 and hsa-miR-27a and their in-common target genes indicated that Wnt, cadherin, integrin and CCKR signaling pathways are more activated in malignant colorectal cancer than normal selected samples. Thus, these dysregulated miRNAs may have a key role in CRC initiation and progression by targeting some of the most important genes in CRC-involved signaling pathways. However, more experimental studies are needed to elucidate exact mechanism of the miRNAs function in CRC-related pathways.

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THE ITERATIVE PROCESS OF QUANTITATIVE MODELING OF INFECTION DYNAMICS IN RENAL TRANSPLANT RECIPIENTS

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Mathematical models play a significant role in providing a numerical and analytical perspective to biological models. When formulating these mathematical models to improve our understanding of biological processes, it is not always possible to find all parameter values in literature. In such cases, and in the presence of data, inverse problems are performed to estimate these unknown parameters. Statistical error models used during inverse problem formulations help quantify the uncertainty and variability that arises with using experimental data. This process of applying mathematical and statistical techniques for modeling physical processes is an iterative one that often leads to new insights following every new iteration. There is a relatively recent research effort in modeling the mechanisms of solid organ transplants, specifically kidney transplants. We present mathematical and statistical models to illustrate the iterative process of modeling for renal transplant recipients infected by BK virus. Using a second order difference-based method to eliminate statistical error model misspecification, we show how modified residuals from the inverse problem can be used to detect discrepancies in mathematical model formulation. Moreover, we illustrate the iterative process of modeling biological processes by improving the current mathematical model to be more biologically accurate.

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METABOLOMICS PROFILING AND THE DECIPHERING OF FRUCTANS METABOLISM IN PLANT TISSUES

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With more than 400,000 plant and 1,000,000 estimated metabolites, metabolomics is an emerging technology that profiles the complete set of small naturally or induced metabolites. The recent progress of metabolmics has led to a comprehensive and global analysis of metabolites and metabolic pathways. Recent development and results have shown that metabolomics approach could be used to deciphere the carbohydrates metabolism and determine the structures of specific metabolites. However, very few works have been reporting on the fructans metabolome during biosynthesis, translocation and accumulation, as well as the source-sink relation. Therefore, broader use of metabolomics will provide comprehensive data sets necessary to model metabolic networks related to fructans metabolism. The goal of this study was to profile the metabolome of fructan biosynthesis in onion plant as model using GC-MS and chemometrics. Results showed that besides conventional sugars, other minor and even one rare sugar was detected during the biosynthesis, accummulation and translocation of sugars. These results indicate that other minor sugars play a role in the biosynthetic and transocatiuon processes of fructans.

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INSIGHTS FROM OLIGOMERIC AND POLYMERIC AUTOPHAGY RECEPTOR COMPLEXES BY ELECTRON MICROSCOPY

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Recently, we showed that autophagy receptor p62/SQSTM-1 assembles into flexible helical filaments. In the current talk, we provide further detailed insights into the molecular basis of polymer formation. Using EM based structure elucidation *in vitro* and *in situ* reveals large oligomeric and polymeric cargo receptor complexes giving rise to higher-order structures that constitute the scaffold for autophagosome formation. The organization of small receptor proteins into helical assemblies provides a cellular mechanism for high selectivity in cargo recognition and a fundamental architecture that enables cargo encapsulation of various sizes from molecular to cellular scale. The presented example illustrates the versatility and synergy of structural and cellular electron microscopy approaches.

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PERSONALIZED DRUG IN THE ERA OF BIG DATA AND PRECISION MEDICINE

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The cytochrome P450 (CYP450) superfamily plays an important role in the oxidation of almost 90% drugs used currently. As variations of single nucleotide polymorphism (SNPs) in human CYP450 genes will cause different drug effects and even adverse effects, studies on SNPs of human CYP450 genes can be used for indicating the most possible genes associated with human diseases and relevant therapeutic targets, predicting the drug efficacy and adverse drug response, investigating individual gene specific properties and then providing personalized and optimal clinical therapies. We have done extensive bioinformatics studies on CYP450 SNPs and its impact on the drug metabolism in the frame work of personalized medicine, i.e., SNPs prediction, the substrate specificity, comparative molecular field analysis, molecular dynamics simulation and QM/MM studies of the metabolic mechanism. Based on the structure of membrane protein targets acquired by bioinformatics tools, and database of molecules extracted from traditional Chinese medicines, various cheminformatics procedures, in the context of network pharmacology, were performed to screen for potential active compounds. A molecule named wgx-50 was obtained, which is an effective component from the Sichuan pepper. Extensive experiments strongly suggest that wgx-50 possesses biologic functions against AD. Discoveries were also made in its potential role in anti-aging.

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STRUCTURAL INSIGHTS INTO THE DYNEIN MOTOR DOMAIN MECHANISM

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The dynein motor protein family, consisting of cytoplasmic and axonemal isoforms, generates movement along microtubules in the minus end direction in eukaryotic cells. Cytoplasmic dynein-1 (dynein-1) carries out most microtubule minus end directed transport and its cargoes include mitochondria, nuclei, as well as protein and mRNA complexes. It also plays important roles during mitosis, where dynein-1 participates in the breakdown of the nuclear envelope and the control of the spindle assembly checkpoint. Cytoplasmic dynein-2 (dynein-2) is involved in the intraflagellar transport in cilia and axonemal dyneins drive the beating movement of the motile cilia subpopulation. Mutations in dynein motors are associated with neurodegenerative diseases, skeletal ciliopathies and primary ciliary dyskinesia. All dyneins exist as multi protein complexes with molecular weights of around 1.4 MDa. They contain a 3500 amino-acid residue motor domain consisting of a ring of six AAA+ domains (ATPases associated with diverse cellular activities), the linker and an elongated coiled-coil helix with the microtubule binding domain (MTBD) at its tip. ATP hydrolysis causes the linker to switch between a post and pre-powerstroke conformation to produce the necessary force for movement. The linker swing is also synchronized with cycles of microtubule binding/release in the MTBD; another important prerequisite for efficient movement. Previously, it was unknown how ATP hydrolysis causes linker remodeling and how this remodeling is correlated with microtubule binding/release. We intend to present two dynein motor crystal structures: dynein-1 from *Saccharomyces cerevisiae* in the apo state and dynein-2 from *Homo sapiens* in complex with the ATP hydrolysis transition state analogue ADP.vanadate. These two structures reveal that ATP hydrolysis causes the AAA+ ring to change from an open to a closed conformation. The closure of the AAA+ ring leads to a steric clash with the linker N-terminal domain, which is subsequently forced to switch from the post- to the pre-powerstroke conformation by a rigid-body movement. AAA+ ring closure also induces a sliding movement within the coiled-coil helix that causes the MTBD to release from the microtubule. The open-to-closed transition of the AAA+ ring is therefore crucial for the coordination of linker swing and the regulation of microtubule binding.

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ZINK BINDING SITE MAPPED ON THE CRYSTAL STRUCTURE OF THE REGULATORY DOMAIN OF THE HUMAN SODIUM-DRIVEN CHLORIDE/ BICARBONATE EXCHANGER

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The sodium-driven chloride/bicarbonate exchanger (NDCBE) is a member of the sodium-bicarbonate co-transporters (NBCs) within the solute carrier 4 (SLC4) gene family and mainly expressed in the brain, especially in the choroid plexus. NDCBE is primarily associated with the presynaptic vesicles of glutamatergic and GABAergic neurons; Zn has been shown to accumulate in presynaptic vesicles of glutamatergic neurons and efflux from the cytoplasm to the vesicle is facilitated by the membrane exporter ZnT-3. The glutamatergic neurons are found cerebral cortex and may be critical for cognitive and emotional functioning. The trace element Zn is vital for life and involved in several functional and catalytic binding sites in enzymes and proteins regulating physiological processes. In the brain, zinc dependent processes include central nervous system development, and neuronal modulation. The crystal structure at 2.8 Å resolution of the regulatory N-terminal domain of human NDCBE represents the first crystal structure of an electroneutral sodium-bicarbonate co-transporter. A novel conserved Zn-binding motif present in the N-terminal domain of NDCBE is identified and characterized *in vitro*. The Zn site is mapped to a cluster of histidines close to the conserved ETARWLKFEE motif and is likely involved with regulation of this important motif. The combined structural and bioinformatics analysis provides a model that predicts, with additional confidence, the physiologically relevant interface between the cytoplasmic domain and the transmembrane domain. As even small variations in concentration of the intracellular Zn would affect the equilibrium between the histidine binding sites and free Zn ions, we hypothesize that this site would consequently act as a pH sensor.

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SEQUENCE ANALYSIS AND MOLECULAR DYNAMICS TO DECIPHER THE ROLE OF C2 DOMAINS FROM PLANT PLASMODESMATA MCTP PROTEINS FOR MEMBRANE TETHERING

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Intercellular communication is critical for multicellularity. Plants have developed remarkable cellular machines such as the plasmodesmata (PD) pores which interconnect every single cell within the plant body, establishing direct membrane and cytoplasmic continuity; a situation unique to plants. A striking feature of PD organization setting them apart from animal cell junctions is a strand of tightly constricted endoplasmic reticulum (ER) called the desmotubule forming the center of plasmodesmata and connected to the PM by tethering elements which appear like spokes by electron microscopy and are assumed to be proteinaceous. Very recently, it was shown by the team of E. Bayer that highly plasmodesmata-enriched proteins, members of the multiple C2 domains and transmembrane region proteins (MCTPs) were significantly more abundant in PD with tight membrane connections, and exhibit the domain architecture expected of membrane tethering proteins, with multiple lipid-binding C2 domains in the N-terminal, and an ER-anchored transmembrane region in the C-terminal region. Our work is focused on investigating the potential docking of C2 domains of MCTPs on the plant plasma membrane at a molecular level. We first performed sequence analysis to accurately define the C2 domains from the MCTP and to obtain good 3D models by homology modeling. Then, molecular dynamics is carried out to predict the docking of the different C2 domains onto biomimetic plant plasma membrane and eventually lipid specificity. Based on these results and sequence analysis, specific binding sites in the C2 domains could be predicted. Our preliminary results suggest that the different C2 domains of MCTP proteins could have different roles in lipid tethering, depending or not of calcium.

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RATIONAL DESIGN OF A TRISPECIFIC T-CELL ENGAGERS (TRITE) CONSISTING OF NANOBODIES 9G8 AND ANTI-CD3 ALONG WITH HLA-A*0201-WT1 FUSION FOR TREATMENT OF EGFR-RELATED CANCERS

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The epidermal growth factor receptor (EGFR) is aberrantly activated by various mechanisms like receptor overexpression, mutation, ligand-dependent receptor dimerization, ligand-independent activation and is associated with development of variety of tumors. Therefore, specific EGFR inhibition is one of the key targets for cancer therapy. Two major approaches have been developed and demonstrated benefits in clinical trials for targeting EGFR; monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs). However, total cure of patients with EGFR-related cancer is still a field of challenge. Although use of bispecific T-cell engagers (BiTE) have previously been introduced as interesting therapeutic platforms, patients with EGFR overexpression/mutation do not still profit from treatment with such antibodies. This might be because of the large size of BiTE antibodies, and thereby, their adverse properties. In this project, for the first time, trispecific Tcell engagers (TriTEs) consisting of nanobodies 9G8 and anti-CD3 along with HLA-A*0201 fused to Wilms' tumor 1 (WT1) peptide epitope were designed for the treatment of EGFR-related cancers utilizing various computational approaches. In agreement with this approach, few reports have also reported for design of trispecific killer engagers (TriKE) in cancer immunotherapy implying an emerging perspective of this strategy in cancer treatment. After analysis of HLA-A*0201 structure presenting WT1 peptide, the main residues involved in interactions with T-cell receptors (TCR) were identified. To generate HLA-A*0201-WT1 fusion, the WT1 peptide was inserted in a region of this HLA-type that caused no significant change in its 3D structures. Subsequently, the nanobodies and engineered HLA-type were fused using optimal Glycine linkers. By using optimal linkers, 3D structure of each nanobody and engineered HLA-A*0201 was preserved. Biological activity of this TriTE was validated *in silico* utilizing molecular docking studies and molecular dynamics simulations carried out by Haddock and Gromacs tools, respectively. This designed TriTE can be highly capable of recruiting T-cells to the EGFR-related cancer cells and subsequently activate their response against cancer cells.

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TRYPANOSOMATIDS PARASITES ACHILLE'S HEEL: TARGETING GLYCOSOME BIOGENESIS

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Trypanosomatid infections are the cause of African sleeping sickness, leishmaniasis, and Chagas disease. The parasites use glycosomes, organelles similar to peroxisomes to compartmentalize glucose metabolism. The malfunction of this compartmentalization releases glucose processing enzymes to the cytoplasm causing runaway glucose phosphorylation, ATP depletion and subsequent cell death. The proteins Pex14 and Pex5 are essential components of the glycosomal import machinery. They bind each other by a direct protein-protein interface. It has been shown that in the absence of Pex14 glucose is toxic to the parasite. We have determined the structure of the Pex14-Pex5 complex to develop a line of small molecule inhibitors able to disrupt the Pex14-Pex5 interaction in a competitive way. The compounds identified proved active against *Trypanosoma brucei in vivo* and in cell-based assays. We have confirmed their disruptive function on parasites glycosomes. Simultaneously, the compounds appear to be of limited toxicity to the human cell lines. Our results confirm that targeting the Pex14-Pex5 interface is a viable therapeutic strategy to treat both human and animal trypanosomiases.

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STRUCTURAL PREDICTION AND ANALYSIS OF PUTATIVE DRUG TARGETS OF SHIGELLA FLEXNERI 2A, THE COMMONEST AGENT OF ENDEMIC SHIGELLOSIS IN DEVELOPING COUNTRIES

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Shigella causes common bacillary diarrhoea in humans which is termed as 'shigellosis'. While ***Shigella dysenteriae*** type 1 causes the most severe form of bloody dysentery and is responsible for outbreaks, ***S. flexneri***, ***S. sonnei*** and ***S. boydii*** causes endemic shigellosis. ***S. flexneri*** 2a is the commonest cause of bacillary diarrhoea in children of developing countries including India. Although not always recommended, antibiotics are used for empirical treatment. However, rapid emergence of antimicrobial resistance has resulted in the bacteria acquiring resistance to most available antimicrobials and therefore there is an immediate requirement of newer drugs effective against this pathogen. The proteome consisting of 4053 proteins of ***Shigella flexneri*** 2a str. 301 was retrieved from NCBI and CD HIT tool was used to remove paralogs/duplicates from the list. The resulting 3178 protein sequences were subjected to Blastp against human proteome to identify protein sequences non-homologous to humans. The resultant 1329 protein sequences were subsequently subjected to DEG Blastp that listed out 620 essential proteins of pathogens and sub-cellular localization were predicted using CELLO v.2.5 tool. 19 were identified as outer membrane proteins among which five (OMP F, thymidine kinase, porin, sorbitol-6-phosphate dehydrogenase, lipopolysaccharide 1,3-galactosyltransferase) were identified as pathogen specific. 3D structure analysis resulted in predicting binding pockets for these proteins which can serve as drug targets. SNP analysis of NGS data showed that the selected target proteins were not vulnerable to non-synonymous mutation during the course of time and therefore ideal candidates to be targeted with novel drugs.

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INTERACTING MECHANISM OF TRANSCRIPTIONAL INHIBITOR PROTEIN ID3 AND TCF4 PROTEIN: MOLECULAR DYNAMICS AND DOCKING APPROACH

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ID3, a member of the ID multigene family of helix loop helix domain can inhibit the regulation of transcription upon protein-protein interaction. DNA binding inhibitor protein has long been characterized as an oncogene that implicates its functional role through its helix–loop–helix (HLH) structure. TCF4 protein which is involved in the transcription regulation is inhibited by ID3 the protein that lacks DNA domain. Our current work aims to identify the functional and physical interaction of this proteins and designing of an aptamer to prevent the interaction of TCF4 and ID3. Network analysis has been performed to predict the inhibitor for ID3. At present there is no three dimensional structure available for these proteins which limits our understanding of its interacting mechanism. We used ***ab initio*** method to build the model from primary sequence. The stability of these proteins and peptide were obtained through MD simulation at 30ns. The integration of PCA and FEL were shown to be a very useful approaches to gain an overall view of the conformational landscape accessible to a protein and helped in the identification of the key residues of TCF4 (Arg 567, Arg 515, Glu 587, Met 590, Gln 519) and ID3 (Glu 36, Asp 43, Cys 47, Arg 50, Arg 60) buried in their HLH motifs which are responsible for dimerization process. All these observations correlate with experimental reports, suggesting that these key residues might play a crucial role in the regulation of transcription and muscle specific genes and cellular signaling pathways controlling proliferation. Thus, the study throws light on the interacting mechanism of ID3-TCF4 and ID3-peptide (ID1/3-PA7) complex and conformational space indicating the key structural changes within the helical regions of the motif.

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A DOCKING MOLECULAL CALCULATIONS TO STUDY THE PROPERTIES OF THE D-MANNOSE AS A NATURAL TREATMENT OF URINARY INFECTIONS CAUSED BY E. COLI

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D-mannose is a natural sugar present in various foods, and binds to *E. coli,* which is then discharged through urine. The purpose of this research is to prove the efficiency of D-mannose and provide an approach to the mean duration of treatment by performing tests on laboratory rats, by provocation of urinary tract infection (UTI). This was done by infecting the rats by different ways and then administration of D-mannose orally. A bacteriological examination of urine was carried out and the interpretation of results was based on the sterility of the culture media. Another aim of this research is the study of protein-protein interactions, which have an important role to understand the process of pathogenesis of bacterial and viral infections. Bioinformatics analysis contributes to the study of protein-protein interactions with the help of softwares for molecular dynamics and protein-protein docking. We have studied the interaction between D-mannose and the FimH protein by using molecular dynamics. Initially, several structural calculations and optimizations by Hyperchem8 software were conducted on D-mannose to understand how the natural sugar attacks the *E. coli* bacterium. Then docking calculations were performed by Hex6.3. Interpretation of results is based on the energy of interaction formed by ligands α-D-mannose and β-D-mannose. The lowest energy of interaction of complex probably presents a greater inhibition of FimH protein.

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SERIAL CRYSTALLOGRAPHY: OPPORTUNITY FOR STRUCTURE-BASED DRUG DISCOVERY ON MEMBRANE PROTEINS

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Application of biophysical and structure-based methods in membrane protein drug discovery projects still represents a significant challenge. leadXpro combines expertise in membrane protein expression, purification, structure determination and application of biophysical methods to facilitate structure-based design of novel medicines. The company has premium access to the synchrotron (Swiss Light Source, SLS), the free electron laser (SwissFEL) and single particle cryo-electron microscopy (University of Basel). Serial femtosecond crystallography (SFX) using X-ray free electron laser (XFEL) significantly increases possibilities of obtaining structural information on membrane proteins. SFX shows a number of advantages for structure-based drug discovery: 1. the ability to determine structures from poor quality crystals shortens the timelines for structure determination and makes some drug targets, such as challenging membrane proteins accessible; 2. higher resolution improves the accuracy of structure determination and interpretation of electron density (more reliable placement of ligand atoms); 3. structural information at room temperature (alone or in addition to cryo structures) gives better insight into protein and ligand conformational dynamics; 4. structures of proteins or ligands with radiation-sensitive groups benefit from minimal radiation damage; 5. the most exciting opportunity of FELs lies with time-resolved analysis of ligand binding and associated protein conformational change. All the benefits will have an impact on the discovery of lead compounds for G-protein coupled receptors, ion channels and transporters.

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