Proceeding

Special Interest Group: Drug-Design

Virtual Meeting, December 1st 2020

ISCB - Regional Student Group Brazil

Introduction

In 2020, we celebrate the twenty years of the first draft of the human genome and its remarkable advancements. This scientific milestone impacted not only our understanding of underlying genetics bases, but also fueled the development of tailored therapies based on human genetic variation. Nowadays, disease treatment could occur according to the interindividual variation in drug responses and therefore stepping toward the personalized medicine concept. In this sense, Drug-Design is a process to develop new molecules that are complementary in shape and charge to the biological target. From clinical assessments to trial, the steps to develop and design a new medication include the target selection, the evaluation of a structure of that target, the pivotal questions to consider in choosing a method for drug lead discovery, and evaluation of the drug leads. The idea of this Special Interest Group arose during the 15th X-meeting - Campos do Jordao Edition, by a small gather of professor and students seeking to open space and foster on the development of new computational methods, partnerships with industries and promote the scientific endeavors and opportunities for bioinformatics in Brazil.

Molecular intervention of SARS-CoV-2 drug targets as potential therapy for COVID-19

The current COVID-19 (coronavirus disease-19) pandemic is caused by the virus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2). Currently, there is no specific treatment capable of treating SARS-CoV-2 infection effectively. While the development of effective vaccines is awaited, intensive global efforts are being made to establish efficient antibodies and to design suitable low molecular weight inhibitors as anti-viral therapies to combat the disease. Genome analysis of coronaviruses and knowledge of the replication cycle of SARS-CoV-2 have been exploited to identify critical components of the pathogen that are appropriate for pharmaceutical intervention. These drug targets include viral structural proteins (Spike,S),virulence factors(nsp1, nsp3c, and ORF7a) as well as proteins involved in viral RNA synthesis and replication like 3-chymotrypsin-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp), papain-like protease (PLpro), and helicase(nsp13). These proteins have therefore been the focus for structure based drug design as well as in silico screening . Using data resources at the EBI ,the three dimensional structures of the proteins have been analysed and forms the basis of this talk which will present an overview of the structure based drug development strategies for COVID-19 and the repositioning of existing therapeutics in fighting COVID-19.

Neera Borkakoti
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Network Medicine approaches for the study of complex diseases and discovery of new treatments

A disease is rarely a consequence of an abnormality in a single gene or cell type but reflects the perturbations of the complex intracellular and intercellular networks that link tissues and organ systems. In the past decade, network medicine approaches have been developed to systematically explore the molecular complexity of a particular disease and its relationship with other phenotypes. The analysis of a comprehensive network of all known physical interactions between human proteins, transcription factors and metabolites, the human interactome, offers the possibility to uncover the biological significance of disease genes, reveal molecular mechanisms that connect different phenotypes, and help identify new pharmacological strategies for disease treatment. In this talk, we highlight the network medicine-based approaches developed in the past years and we show their applications for the understanding of diseases, and for the development of new therapeutic and prevention strategies.

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Associate Research Scientist

Targeting proteases to treat neglected and emerging diseases

R. Salgado is Ph.D. in Chemistry and Biological Chemistry from University of California San Francisco, USA. Since 2011, she is affiliated to the Department of Biochemistry and Immunology at UFMG, where she applies computational techniques and experimental assays to development of new ligands and therapeutic targets. Recently, she was awarded with the prizes: “L’Oréal-UNESCO-ABC Para Mulheres na Ciência 2017, Categoria Química” and “L’Oréal-UNESCO For Women in Science International Rising Talent 2018”.

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Data fusion in drug-target interaction prediction for drug repositioning

Identifying drug-target interactions is a crucial step in drug repositioning, the process of suggesting new indications for known drugs. There are about 9000 FDA-approved and experimental small molecule drugs and more than 500.000 protein records available. Performing in vitro experiments would be too expensive and time-consuming to check all the putative drug-target couples, therefore computational techniques might help to predict compound biological activity (IC50) and suggest new putative medical indications for existing drugs. Machine learning techniques such as Bayesian matrix factorization and deep neural networks can integrate structural information of drugs, proteins and their binding to better predict biological activity and suggest new drug-target interactions, with a big impact on the drug discovery process. Different kinds of side information can be used to help the prediction process, such as chemical structures of the drugs, 3D structures of the protein targets or phenotypic effect of drug-target interactions. In my work I analysed the contribution brought by different kinds of heterogeneous information in the prediction process, taking into account different modalities of validation, as well as advantages and difficulties related to the application of each specific type of data.

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Lightning Talks

Virtual screening of substances with potential antiviral activity against three flaviviruses: dengue virus, yellow fever virus and zika virus

Mateus Serafim
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Phenotypic screening of compounds enriched by molecular docking to protein kinase targets in schistosoma mansoni

Naiara Clemente Tavares
Instituto René Rachou - Fiocruz MG

Arg2 SNPs associated with HBF response in patients sickle cell anemia treated with hydroxyurea

Bárbara Nogueira
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Construction of a nanoparticle based on a synthetic virus-like protein with chemotherapy potential

Amanda Patrícia Gonçalves
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Metformin regulates cells epigenomic landscape leading to decreased proliferation and inflammation in hepatocytes

Izabela Mamede Costa Andrade Conceição
Universidade Federal de Minas Gerais

In-silico approaches for mycoplasma pneumoniae multi-epitope vaccine construction

Thaís Cristina Vilela Rodrigues
Universidade Federal de Minas Gerais

Poster Tracks

Computer-Aided Drug Design (CAAD)

Derivated of dibenzoylmethane: *In silico* analysis for drug development

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In silico analysis is the beginning of many researches and it can predict which way follow it's possible to evaluate the promisor compounds and the pathways of action. Most drugs for the treatment of cancer have limited efficacy and tumor recurrence rapidly follows. Therefore, the search for new molecules is necessary for the development of more effective clinical therapies. The family of beta-diketones, including dibenzoylmethane, is known by the large bioactivity, such as antitumor, antibacterial, and anti-inflammatory activities. Based on this, the aim of this study was evaluating in silico the derivate of dibenzoylmethane (ABB), one beta-diketone, as pharmacokinects, physicochemical and toxicity by ADMET and bioactivity score methods to a drug development. Using the web platforms Molinspiration Cheminformatics to draw the molecule and generate the SMILES code to run the bioactivity score and the preADMET and pkCSM to check the pharmacokinetics, physicochemical and toxicity, was possible to check all the parameters and use the Lipinski's rule of five (Ro5) to validated the drug design. According to Ro5 the physicochemical parameters of this molecule was adequous to continue the drug-likeness. The evaluation of inhibitory effects of cytochrome p450 isoforms (CYP), known by monooxygenase family of enzymes, indicates that ABB isn't an inhibitor of CYP1A2 and CYP2D6, but it inhibits the CYP2C1, CYP2C9 and CYP3A4. Those results show that ABB should be metabolized normally. In complement the test of mutagenicity of ABB showed negative for mutagenicity and carcinogenicity. The risk of hERG I inhibition was negative while for hERG II it was positive, indicating a low cardiotoxicity. In Molinspiration bioactivity score all the points checked were between -5 and 0 that shows a moderate bioactivity. These results showed that the ABB compound has great potencial to provide us with a potent drug in medical clinic and in vivo tests should be performed.

Keywords: Beta-diketones, Bioactivity, Drug-likeness

Optimization of SMTGR inhibitors using a fragment-based drug design (FBDD) approach

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Schistosomiasis is a neglected tropical disease caused by Schistosoma spp. Praziquantel (PZQ) is the unique drug used for the treatment of the disease. Despite the success of the treatment, the concern about the emergence of strains less sensitive to PZQ, and the possibility of evolution of drug resistance are growing. Thioredoxin glutathione reductase of Schistosoma mansoni (SmTGR) is a validated drug target that plays a crucial role in the redox homeostasis of the parasite inside the human host. The Fragment-based Drug Design (FBDD) strategy consists of screening low molecular weight compounds against macromolecular targets (usually proteins) of clinical relevance. These small molecular fragments can bind at one or more sites on the target and act as starting points for the development of lead compounds. An FBDD screening campaign was performed obtaining 32 fragments that bind to 8 sites located at the SmTGR surface. From those sites, one secondary site was selected and fragments that bind to that site were optimized using a fragment-growing approach. The optimization was performed using the program AutoGrow 3.0. A total of 42 new ligands were generated from the initial fragments.

Keywords: FBDD, schistosomiasis, fragment-growing

Molecular docking and dynamics study of natural compound for potential inhibition of main protease of SARS-CoV-2.

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Newly emerged SARS-CoV-2 made recent pandemic situations across the globe is accountable for countless unwanted death and insufferable panic associated with co-morbidities among mass people. The scarcity of appropriate medical treatment and no effective vaccine or medicine against SARS-CoV-2 has turned the situation worst. Therefore, in this study, we made a deep literature review to enlist plant-derived natural compounds and considered their binding mechanism with the main protease of SARS-CoV-2 through combinatorial bioinformatics approaches. Among all, a total of 14 compounds were filtered where Carinol, Albanin, Myricetin were had better binding profile than the rest of the compounds with having binding energy of –8.476, –8.036, –8.439 kcal/mol, respectively. Furthermore, MM-GBSA calculations were also considered in this selection process to support docking studies. Besides, 100 ns molecular dynamics simulation endorsed the rigid nature, less conformational variation and binding stiffness. As this study, represents a perfect model for SARS-CoV-2 main protease inhibition through bioinformatics study, these potential drug candidates may assist the researchers to find a superior and effective solution against COVID-19 after

Keywords: Protease inhibitors; phytochemicals; virtual screening; binding modes; MD simulation.

HTP SurflexDock 1.2: Improving SBVS campaign by including the post-processing stage

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Structure-Based Virtual Screening (SVBS) is an essential tool that may be used to delimit a sub-set of the more specific inhibitors for a receptor of interest during the early stages of drug discovery studies. We developed the HTP SurFlexDock, a web server that improves SBVS campaigns by the use of ensemble docking pipeline in order to simulate the protein receptor flexibility. However, like other SVBS tools, HTP SurflexDock uses a scoring function based on the ΔG of the best pose to classify the compounds. This function is subject to enrich poses with unnatural artifacts such as improper ligand torsions and malformed hydrogen bonds, among others. In this sense, we include a post-processing phase in the HTP SurflexDock, where the user can select up to 10 promising compounds from the initial classification to boost the exploratory of the active site conformational space. At this stage, the user is presented with up to 30 more poses per complex using AutoDock 4.2. Through qualitative analysis of the three-dimensional interactions of the obtained complexes in ensemble docking, the users takes a better picture of the sub-set of the compounds with better interactions and consequently choose the compounds that will go to future stages of the nest drug discovery experiments with greater fidelity. The HTP SurFlexDock is freely available as a web service or download at http://biocomp.uenf.br:81.

Keywords: Drug Discovery; Structure-Based Virtual Screening; Ensemble Docking

Drug-repurposing

Construction of a nanoparticle based on a synthetic virus-like protein with chemotherapy potential

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Cancer is a devastating disease whose treatment tends to be very aggressive due to its side effects and low selectivity. Nanotechnology has emerged as an alternative in medicine, especially in cancer treatments. In this case, molecular tools can be used to enhance chemotherapy delivery-drugs nanoparticles, making them more selective. DNA molecules have been suggested as a great material for nano-constructions once it can be associated with some chemotherapy molecules such as doxorubicin and cisplatin. In 2014, Hernandez-Garcia and colleagues designed the C4S10K12 protein, a synthetic viral coat protein which self-assembles with dsDNA molecules forming rod-shaped virus-like nanoparticles. Based on these insights, we designed a biopolymeric doxorubicin-carrier nanoparticle coated by the C4S10K12 protein and evaluated its stability in physiological conditions as well its internalization, cytotoxicity and selectivity on murine melanoma tumor cells lines. Through non-denaturing electrophoresis we demonstrated that DNA molecules remain intact in physiological conditions and can tolerate the action of DNAse enzyme. Fluorescence Microscopy showed that the constructed nanoparticle can enter melanoma murine tumor cells after 1 hour of treatment and release its content inside those cells after 12 hours. This controlled and delayed release caused an increase in doxorubicin cytotoxicity when compared to non encapsulated-doxorubicin treated cells, which was demonstrated through MTT assays. These experiments also showed that the DNA-Doxorubicin complex coated by C4S10K12 was more toxic to tumor cells than to non tumor cells, which did not occur in non encapsulated-doxorubicin treatment. These results show that our construction is a stable nanoparticle capable of entering tumor cells in vitro, triggering increased cytotoxicity and selectivity. These features demonstrate that these nanoparticles have a high potential for chemotherapy and open new perspectives to study drug-targeting in tumor microenvironments.

Keywords: Nanotechnology; Drug-repurposing; Cancer; Virus-Like Particles

Drug-gene expression profiles and systems biology approach to identify repurposed drug candidates for targeting sclerostin in peri-implantitis disease.

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Successful identification of a therapeutic strategy to treat patients with periimplantitis remains extremely important as post-implant bone degradation leads to implant failure and extreme bone loss. Given that the establishment of a new drug is quite expensive and time-consuming, the drug repurposing approach has come in handy. It helps to identify the experimental drugs that are beyond the purview of the initial clinical indication. In our current study, we propose a three-step drug repurposing approach in treating peri-implant bone defects and investigating the action of the FDA approved drugs to inhibit the key protein Sclerostin, involved in bone degradation. As the preliminary step, we differentiated the gene expression pattern in periimplantitis and dentate patients with their drug-induced profiles to identify the primary lead candidates. As the second step, we employed the computational biology approach to evaluate the protein-drug interaction and segregate the best hits among the identified lead compounds for sclerostin. Finally, the mode of action network for each candidate is established with the help of literature support, and the drug enrichment and pathway analysis are performed on the target genes in the network to evaluate the drug efficacy. This approach provided us with a drug interaction profile and specific genes and biomarkers to target bone mineralization in peri-implantitis. Thus, our three-step drug repurposing method is consistent with identifying the drug molecules with high efficacy and developing an efficient therapeutic strategy to treat peri-implantitis.

Keywords: sclerostin; drug repurposing; drug gene interactions; drug design; periimplantitis

Virtual screening using approved drugs: *in-silico* evaluation of anti hat potentials

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Human African Trypanosomiasis (HAT), also called sleeping sickness, is a neglected disease caused by the parasite Trypanosoma brucei. The problem with HAT is that the drugs used in the treatment have several adverse effects (personality changes, psychosis and hyponatremia), negatively influencing therapeutic adherence. The objective of the work is to find potential substances that can act by inhibiting the 24-c-sterol-methytranferase (SMT) protein, which participates in the ergosterol biosynthesis, an important metabolic pathway for the parasite. First, the PDBid structures were prepared: 3BUS (a transferase of Lentzea aerocolonigenes, used in the prediction of the TbSMT model) and the SAH cofactor (S-Adenosyl-L-homocysteine). We used PDB2PQR web server for protonation of 3BUS (Amber force field) and OpenBabel was used for the ligand, both at pH 7.4. The addition of hydrogens, addition of Gasteiger charge and Grid formulation (center x: 15.278; y: 28.139; z: 30.662; and size x: 60; y: 60; z: 54;) was done using AutoDock Tools and Chimera . For redocking, the AutodDock Vina was used, testing 12 different exhaustiveness. The result that had the lowest RMSD (calculated with OpenBabel) was exhaustiveness 48, 1,355 Å. With the parameters validated, the docking was done between the TbSMT structure (obtained through previous work) and the shape of the cofactor before the action of the enzyme, SAM (S-Adenosyl-L-methionine). For this, SAM was removed from the PDBid: 4DF3 crystal (a transferase of Aeropyrum pernix). With the SMT structure containing the SAM cofactor, virtual screening was performed using a database present at ZINC, World. We found 10 promising substances classified by binding energy.
Submitted:

Keywords: HAT; Ergosterol biosynthesis; Drug-repurposing; New treatment

Epigenetics

Metformin regulates cells epigenomic landscape leading to decreased proliferation and inflammation in hepatocytes

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Metformin is the first-line therapy for type 2 diabetes, and is also approved for other diseases, including cancer. Metformin's mechanism remains not known, with its anti-aging, anti-carcinogenic, and epigenetic-regulator effects not thoroughly understood. We propose mechanisms for metformin's beneficial effects on inflammation and proliferation, by altering the expression of transcripts that act as epigenetic regulators. We analyzed high-throughput RNA-seq data of human hepatocytes treated with metformin using Salmon for transcript quantification, DESeq2 for differential expression, followed by fgsea and txGeneNetwork for network-based functional enrichment. We selected transcripts that acted as epigenomic regulators and queried their translated sequences for the presence of whole domains using Pfam and InterProScan. From all differentially expressed transcripts (DETs), six code for proteins containing functional domains that could act as regulators in epigenetic pathways. Four DETs belong to the histone-lysine-demethylase (KDM) subfamily containing the JumonjiC (JmjC) domain that converts α-ketoglutarate (α-KG) to succinate during demethylation. High succinate levels inhibit α-KG conversion, and metformin is known to reduce succinate levels, leading to increased KDMs expression. KDM gene expression was linked to proliferation, but not at the transcript isoform-level, and KDMs isoforms that contained the JmjC domain showed anti-carcinogenic effect. Conversely, short KDMs isoforms which increase proliferation lost the JmjC domain through alternative splicing. Two DETs were downregulated isoforms of Methionine-Adenosyltransferase 2A (MAT2A). MAT2A is the leading converter of S-adenosylmethionine (SAM), a cellular donor of methyl groups, that is mostly expressed in extra-hepatic tissues. Its paralogue, MAT1A is present in hepatocytes, where a switch in MAT1A:MAT2A ratio is positively correlated to hepatocellular carcinoma and liver fibrosis. Metformin downregulating those transcripts leads to increased SAM levels and enhances DNA methyltransferases activity. Our findings highlight an epigenetic regulatory axis controlled by isoform-specific differential expression induced by metformin, and unravels novel metformin's roles on hepatocytes and target pathways for hepatic disorders.

Keywords: Metformin; Epigenetics; Cancer; Inflammation; RNA-seq

Molecular Docking and Optimization potentials of some phytoligands from *Ficus sycomorus* Fraction inhibiting *Anopheles coluzzii* Cytochrome CYP6P3 enzyme

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A major obstacle in controlling malaria is mosquito's resistance to insecticides, including pyrethroids. The resistance is mainly due to over-expression of detoxification enzymes such as Cytochrome P450. Insecticides tolerance can be reduced by inhibitors of P450s involved in insecticide detoxification. The ligand efficiency (LE) indexes were used as criteria in drug discovery and development decisions especially in fragment-based drug design (FBDD) perspective for efficient fragments optimization. Molecular docking study and computational modeling were employed using Glide XP software to determine the inhibitory potentials of some phytoligands isolated from *Ficus sycomorus* against *Anopheles coluzzii* P450 isoforms, CYP6P3, implicated in resistance. Homology model of the P450 enzyme was constructed using the Crystal structure of retinoic acid bound cyano bacterial CYP120A1 (PDB ID: 2VE3; Resolution: 2.1 Å). Potential LE and properties for optimization into formidable P450s inhibitors were analyzed using standard mathematical models. Compounds 5, 8 and 9 bound to the Heme iron of CYP6P3 at a distance of 3.14 Å, 2.47 Å and 2.59Å respectively, showing potential site of metabolism. The binding energies were 8.93, 10.44 and 12.56 Kcal/mol respectively showing non spontaneous interaction with the enzyme active site. The most common amino acid residues in the binding pocket were hydrophobic Phe123, Val310, Pro379 and Val380. These inhibitors were probably act by reversibly coordinating with the prosthetic heme iron atom and formation of quasi-irreversible complexes with the iron of the heme prosthetic group. The coordination of a strong ligand to the heme iron shifts the iron from the high- to the stable low-spin form and prevented oxygen binding to the heme. This change in the spin state occurs concomitantly with a change in the redox potential of the P450s, which eventually inhibit the catalytic activities. The LE index showed high potential of these compounds to form core fragment for optimization into a potent P450s inhibitors.

Keywords: Binding energy; CYP6P3; GLIDE; Inhibitors; ligand efficiency; Optimization

Molecular modeling of butyrylcholinesterase inhibitors as potential drugs against alzheimer's disease

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Alzheimer's disease (AD) is the most prevalent neurodegenerative disease worldwide. According to the World Health Organization (WHO), it is estimated 152 million people worldwide will be affected by AD in 2050. Memory loss, a symptom of AD, is the result of a decrease of acetylcholine level in the brain, due to the increase in cholinesterases, mainly butyrylcholinesterase (BChE). Our study targets new potential BChE inhibitors, by molecular modeling, aiming to alleviate the symptoms from the acetylcholine deficit. We used two 3D structures of human BChE complexes with potent inhibitors, resolved by X-ray diffraction and available in the Protein Data Bank (PDB): 5DYW and 5NN0 (Košak et al., 2016, 2018). The inhibitors have a piperidine heterocycle showing (R) configuration at C3 of the piperidine ring, whose amino group is protonated, according to Košak et al. (2016, 2018). The construction of the 3D structures of the inhibitors (5HF601 in the 5DYW complex and 92H627 in the 5NN0 complex) was carried out in the Spartan'14, followed by geometry optimization and conformational analysis (systematic and random), using the MMFF94 force field. Molecular docking/redocking was performed on the DockThor server (https://dockthor.lncc.br/v2/), where the C-alpha from Gly116 (chain A) at the active site, was chosen as the center of the 20x20x20 Å box. The preliminary results indicate that, for both ligands, the poses with the best score refer to the structures where the absolute configurations of both, C3 and N of piperidine, are (S). In the case of C3, according to Košak et al., the configuration is (R), while the configuration of the protonated N is not described, probably due to the possibility of both configurations coexisting in equilibrium. Thus, our study suggests re-evaluating the configuration of these stereogenic centers. As a perspective, we will study the binding modes of other inhibitors.

Keywords: Alzheimer disease; Butyrylcholinesterase; Molecular docking; Molecular modelling; Design drugs

In-silico Evaluation of Some Flavonoids Honeybee Constituents as SARS-CoV-2 Main Protease (COVID-19) Inhibitors

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The huge attack of coronavirus disease (COVID-19) over all the world forces the researcher around the world to study the crystal structure of the main protease Mpro (3-chymotrypsin-like cysteine enzyme) which is the essential enzyme for coronavirus. The inhibition of this enzyme active site becomes the target of all scientists of drug discovery to overcome this disease. On the bases of this view, using the molecular modeling approach to evaluate the effect of different flavonoids compounds from honeybee and propolis as SARS-CoV-2 main protease inhibition using Schrodinger Maestro v10.1. The presented study resulted in six main compounds possess high binding energy with the receptor active site of COVID-19 main protease. Developing this study aim to be an effective way for the honeybee constitution as an inhibitors ligand for SARS-CoV-2 main protease inhibition and be in the medicinal study of anti-COVID-19 therapeutic drugs.

Keywords: Honeybee; Molecular docking; flavonoids; SARS-CoV-2; Structure activity relationship (SAR)

Phenotypic screening of compounds enriched by molecular docking to protein kinase targets in schistosoma mansoni

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Schistosomiasis is a helminthiasis caused by parasites from the Schistosoma genus. This disease presents a high morbidity index and its treatment is based only on praziquantel administration. Yet, due to limitations as low efficacy in parasites' immature stages and worms with reduced sensitivity, studies to directing new therapeutic approaches are required. The discovery and development of a new drug have a high cost and demand several years of research. Therefore, the initial identification of a potential target, followed by the screening of molecules, provides a crucial advance at the beginning of the drug discovery process. In this context, functional studies of the PKs SmERK1, SmERK2, SmFES, SmJNK, and Smp38 pointed out that those proteins are involved in Schistosoma mansoni maturation, reproduction, and survival, indicating that they can be promising drug targets for schistosomiasis treatment. Accordingly, this work search for new alternative molecules to support schistosomiasis treatment. Hence, three-dimensional structures of the kinase targets were predicted and molecular docking was employed to identify molecules from the Managed Chemical Compound Collection that could be capable to bind to the ATP binding site of those PKs. Then, 169 molecules were selected to perform an in vitro screening in schistosomula and adult worms. Following, the in silico analysis of ADMET properties was conducted for the compounds. After the in vitro screening, 52.1% of the selected molecules induced viability reduction in S. mansoni and were considered as active compounds, being 10.1% active only in schistosomula, 30.8% in adult worms, and 11.2% in both stages. Moreover, 36.7% altered the schistosomula area. In conclusion, the prioritization of molecules through a rational model was efficient, since a high number of active molecules were identified. Additionally, it was possible to point-out potential molecules to be used in future trials in search of a new schistosomiasis treatment.

Keywords: Schistosoma mansoni; protein kinases; drug screening; molecular docking

The HGPRT and XPRT ENZYMES from *Leishmania donovani*: molecular modeling and study of dual inhibitors.

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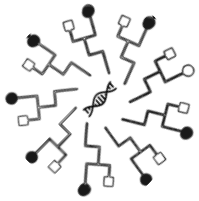
Hypoxanthine-Guanine Phosphoribosyltransferase (HGPRT) and Xanthine Phosphoribosyltransferase (XPRT) are classified in the type I PRTases family, which are responsible for purine recycling in the organism to which they belong. Protozoans of the order *Kinetoplastidae* such as *Leishmania spp*. cannot make de novo purine synthesis, and they have only the recovery route. The aim of this work was to perform molecular homology modeling of both HGPRT and XPRT targets, as well as to perform a virtual screening in order to search dual inhibitor for both enzymes. The 3D structures of HGPRT and XPRT from *Leishmania donovani* (Laveran and Mesnil, 1903) were constructed by the Swiss-Model Workspace, considering the best available crystallographic templates for both targets. The ROCS program (Openeye Scientific Software) was used to develop five pharmacophore structures, which were based on five active compounds for type I PRTases. Then, we submitted the pharmacophore structures to a ROCS searching a database of 57,000 compounds from natural sources extracted from ZINC DATABASE, in which a total number of 1,825 compounds (hits) for the five pharmacophores were returned. In a second step, we performed a receptor-based virtual screening (RVBS) using AutoDock Vina for molecular docking calculations. The 50 best compounds for both enzymes obtained affinity energies between -8.4 and -10.9 Kcal/mol, of which ZINC4096947, ZINC519733, ZINC485610, ZINC2150030 and ZINC58116 presented best values for both enzymes, as well as Lipinski's rule of five characteristics. Molecular dynamics calculations revealed that the compound ZINC2150030 remained within the active site of both enzymes after 50 ns. Additionally, this inhibitor candidate can be tested in vitro and in vivo as a new treatment option for leishmaniasis.

Keyword: *Leishamia donovani*; Virtual Screening; Molecular Dynamics



Network of possible targets with clinical-pharmacological potential around the compounds identified in *Syzygium cuminititle* of abstract

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Originally from Asia, *Syzygium cumini is* part of the *Myrtaceae* family and is currently part of the Brazilian Cerrado. This plant is gaining notoriety through the potential clinical-pharmacological effects of extracts made from its parts and compounds identified in its composition. A comparative analysis of the 2D and 3D structure of the compounds allows its chemical association with possible biological targets involved in metabolic pathways related to diseases. Besides, an investigation of the relationship between the targets helps to elucidate some functions to establish a priority for the compounds according to the degree of involvement in metabolic pathways. To enhance the biodiversity of the Cerrado and present a range of biotechnologically interesting S. cumini compounds, the molecular structures of the compounds were collected in the Pubchem database and prepared in the molecular modeling software VIDA 4.4.0. These compounds were inserted in the Swisstargetprediction platform, which searches 2D and 3D similarity targets from a small molecule. The interaction between the targets was analyzed in the STRING 11.0 platform and the degree of involvement with the metabolic pathways included in the DAVID 6.8 platform. As a result, a network of interactions was prepared with the help of the Cytoscape 3.8.0 software, thus gathering valuable information for potential drug research. The results of the correlations made between the compounds and the metabolic pathways indicated influence in diseases such as lung cancer, bladder and breast cancer, chronic obstructive pulmonary disease, and among others. This work will facilitate the evolution of studies involving these diseases and will also provoke the search for new effects for the extracts made from the parts of S. cumini.

Keywords: *Syzygium cumini;* Network Phamacology; Brazilian Biodiversity; *Myrtaceae*

In silico approaches for *Mycoplasma pneumoniae* multi-epitope vaccine construction

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Pneumonia is a serious health problem with global effects, being the death cause of over one million people annually. Among the main microorganisms responsible by pneumonia, *Mycoplasma pneumoniae* is one of the most common, with a significant increase in the last years. The vaccines are fundamental in diseases prevention besides to considerably avoid the need of health services and funding resources. In this way, the proposal of the present study is to construct through immunoinformatic tools, a multi-epitope vaccine against M. pneumoniae. Multi-epitope vaccines are constituted by epitopes properly selected to induce targeted immune responses and avoid adverse reactions. First the core proteins were previously determined through reverse vaccinology, then the search for MHCI, MHCII and B epitopes were performed as well as the check for overlapping epitopes, capable to induce both humoral and cellular responses. Those epitopes were filtered according to their immunogenicity, population coverage, among others. The final epitopes were joined with heat-labile enterotoxin from Escherichia coli as adjuvant and the structure of the vaccine was predicted. The vaccine was considered physically stable, non-toxic, non-allergen, not significantly similar to human proteome and with appropriate antigenic and immunogenic properties. The molecular docking of the vaccine with the Toll-Like Receptor 2 was performed as well as the dynamic simulation to ensure the affinity and stability between this complex. In silico cloning was tested in an expression vector with positive results. In addition, the immune simulation for vaccine efficacy will be test. Through immunoinformatic approaches we constructed an effective multi-epitope vaccine candidate, that with further tests could contribute to prevention of pneumonia in a massive scale. Besides that, the study assists to better understanding of the immune mechanisms regarding *M. pneumoniae* infections and its interaction with the host.

Keywords: Multi-epitope vaccine; Vaccine; *Mycoplasma pneumoniae;* Immunoinformatics Dynamics Simulation

A new approach to research therapeutic targets for triple negative breast cancer: investigation of the association between tumor genome amplified regions and competing endogenous rnas networks

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Breast cancer (BC) is the second most common type of cancer in women in Brazil. By immunohistochemistry, BC is divided into four subtypes, among which the Triple Negative (TN) is the most aggressive. This subtype has no specific diagnosis or therapy. Thus, the research of therapeutic targets and biomarkers for TN BC is encouraged. It is known that competing endogenous RNAs (ceRNAs) networks are RNA-miRNA-RNA interaction networks that result in gene expression modification. Copy number alterations (CNAs) are gain or loss changes of chromosomal segments. We hypothesize that genome amplified regions in TN tumors may stimulate the formation of ceRNAs networks; this association's investigation may be an alternative strategy for researching TN BC biomarkers and therapeutic targets. We aimed to identify potential ceRNAs transcribed in TN tumors genome amplified regions and explore this mechanism's potential in the TN BC carcinogenesis regulation. A previous study realized by the research group identified CNAs in TN (n = 29) and Non-Triple Negative (n = 16) breast tumors using array-CGH. With this data, we performed a computational prediction of ceRNAs networks between transcripts from genome amplified regions in TN tumors and transcripts from the total transcriptome of Basal tumors (a molecular BC subtype, considered correspondent to TN in this study) – using the GDCRNATools package in the R software. We found a possible network of 8 pairs of overexpressed ceRNAs (logFC> 0.58, p-value ≤ 0.01, and positive correlation). Present in this network, TMPO-AS1 is a lncRNA with oncogenic functions already validated. The mir-302 and mir-520 miRNA families, described as tumor suppressors in the literature, are the most frequent in our network. The ceRNAs network around TMPO-AS1 and the most frequent miRNA families present themselves as potential candidates for specific TN BC therapy – showing that our analysis strategy can be an alternative to traditional research methodologies.

Keyword : breast cancer; CNAs; ceRNAs; therapeutic targets

Personalized Medicine

CCOMPUTO – Collaborative computational tools for Dutch molecular tumor boards

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Advances in genomics techniques allowed the analysis of big sets of cancer patients what lead to the identification of mutations, showing a pattern shared by cancer patients. These mutations are often responsible for drive signaling pathways essential for malignant cells' survival. Within the large number of patients who benefit from these genomics techniques, individuals harboring Non-Small Cell Lung Cancer (NSCLC) are the most favored by, due to the presence of mutations on enzymes such as the Epidermal Growth Factor Receptor, Anaplastic Lymphoma Kinase, Kirsten Rat Sarcoma GTPase or the BRAF serve as a biomarker for treatment regiments with kinase inhibitors. The success of kinase inhibitors is linked to the presence or absence of a specific subset of mutations widely described in the literature. However, medical times are often challenged with mutation of unknown significance and/or impact on drug binding. Seeking to provide fast identification of mutational impact in the available treatments, Dutch University Medical Centers assembled Molecular Tumor Boards (MTB) where challenging patients flaunting novel mutations can be analyzed under the lights of a personalized medicine approach. Besides involving medical doctors and geneticists, the MTB from the University Medical Center of Groningen (UMCG) also relies on the use of computational biology for rapid assessment of such mutational landscape. In this work, we present how classical tools from computational biology are applied daily in the context of drug screening in the presence of novel mutations and the impact this approach has on patient survival.

Keywords: Molecular Tumor Board; Personalized Medicine; Kinase; Kinase Inhibitor

Pharmacogenomics

NAMPT SNPs associated with VISFATIN/NAMPT levels located nearby a putative enhancer region activated by metformin

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Nicotinamide phosphoribosyltransferase (NAMPT) is a potential therapeutic biomarker or target for several diseases. NAMPT is activated by Metformin, the first-line therapy for type 2 diabetes, and it is also used as a treatment for other diseases. Moreover, the single nucleotide polymorphism (SNP) rs1319501 in NAMPT promoter region were found to be associated with plasma NAMPT levels, and tightly linked with the SNPs rs9770242 and rs61330082, which are located ~1,500bp upstream from the NAMPT transcription start site. However, these noncoding SNPs may overlap with functional regulatory elements, such as enhancers. Thus, we searched for metformin-responsive regulatory elements in the NAMPT locus, and linked SNPs within them which may be associated with NAMPT levels. First, we examined publicly available ChIP-seq data for active (H3K27ac) and silenced (H3K27me3) histone marks on human hepatocytes treated with metformin, GeneHancer to identify active regulatory elements (enhancers and promoters), and several cis-regulatory elements assignment tools from the Encyclopedia of DNA Elements (ENCODE) to identify enhancers around the NAMPT locus. Next, we performed the functional annotation of noncoding SNPs located in the NAMPT locus using the Genotype-Tissue Expression (GTEx) project data for SNPs linked to NAMPT expression. The SNPs rs1319501, rs9770242 and rs61330082 overlap with a metformin-responsive region enriched for the active histone mark H3K27ac upon metformin treatment, which is located nearby an enhancer element according to GeneHancer (GH07J106288). Interestingly, rs61330082 and rs11977021 were in perfect linkage disequilibrium in a cohort of severely obese children and are associated with visfatin level and adverse cardiometabolic parameters. According to GTEx, these SNPs are eQTLs for NAMPT expression in heart tissue. These data support that noncoding variation within a metformin-activated enhancer may increase NAMPT expression. The perspectives are to functionally characterize these noncoding NAMPT SNPs, which could help to predict NAMPT levels in patients with type 2 diabetes treated with Metformin.

Keywords: Visfatin/NAMPT levels; NAMPT gene polymorphisms; Functional annotation; Metformin; Type 2 Diabetes

ARG2 SNPs associated with HBF response in patients sickle cell anemia treated with hydroxyurea

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Sickle cell anemia (SCA) a β-hemoglobin disorder, and fetal hemoglobin (HbF) ameliorates clinical severity of SCA. Hydroxyurea (HU) is the main drug used to treat SCA patients, which improves their clinical course by raising HbF levels. HU was suggested to act as a nitric oxide (NO) donor in SCA. Recently, HU was shown to modulate red blood cell (RBC) NO signalling pathway, RBC rheology and oxidative stress through its effects on HbF and possibly on NO delivery. However, the HU NO-related effects on RBC physiology and NO signalling pathway are not fully known. While BCL11A and HBS1L-MYB are the major loci regulating HbF levels, other candidate genes were associated with significant changes in HbF levels in SCA patients treated with HU, including two ARG2 intronic SNPs (rs10483801 and rs10483802). Therefore, these SNPs may be linked with the actual functional regulatory elements. Here, we performed the identification of cis-regulatory elements at ARG2 locus using several assignment tools, including The ENCyclopedia Of DNA Elements (ENCODE) ChIP-seq data for the active histone mark H3K27ac, the ENCODE registry of candidate cis-regulatory elements (cCREs) using SCREEN (https://screen.encodeproject.org/). Next, we performed the functional annotation of these intronic ARG2 SNPs using the GenotypeTissue Expression (GTEx, www.gtexportal.org/home/) project and the RegulomeDB (https://regulomedb.org/). Notably, rs10483801 and rs10483802 SNPs are located ~400 bp distant in the last intron of ARG2 and they overlap with H3K27ac peaks for three ENCODE cell lines, namely K562, NHEK and NHLF. Moreover, they are linked to transcription factors and are located next to a region with proximal enhancer-like signature identified by the ENCODE registry of cCREs. These data support the presence of an enhancer element in the last intron of ARG2. Notably, in SCA hemolysis results in the release and activation of arginase, an enzyme that reciprocally regulates NO synthase activity and thus, NO production.

Keywords: ARG2; polymorphisms; Fetal hemoglobin; Hydroxyurea; Sickle cell anemia

Warfarin dose prediction through a user interface using clinical, demographic and pharmacogenetic data

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We work on a user interface (UI) designed to assist in warfarin therapy by predicting a best therapeutic dose, calculated from the data entered into the UI. It will be able to predict more accurate doses for patients diagnosed with atrial fibrillation, stroke, thrombosis or heart valve prosthesis in whom it is desired to maintain an international normalized ratio (INR) between two and three, using their clinical, demographic and pharmacogenetic data. The prediction models that were considered for the construction of this prediction interface were the International Warfarin Pharmacogenetics Consortium (IWPC), multiple linear regression, regression using regularizers (Lasso regression, Ridge regression), Elastic net regression, regression of selected variables by AIC, Ridge Regression with Variable Selection (foba package in R) and a simple neural network model that consists of 3 hidden layers of 100 neurons each, using data from patients of the Brazilian Heart Institute (InCor - USP). This data include clinical, demographic, and pharmaceutical factors and and risk genotypes of the cytochrome P450 2C9 (CYP2C9), vitamin K epoxy reductase (VKORC1), leukotriene B(4) omega-hydroxylase 1 (CYP4F2) and NAD(P)H dehydrogenase (quinone) 1 (NQO1) genes. The models were trained with the information of 614 individuals, which reached INR values between 2 and 3 when receiving a maintenance dose of warfarin, and tested in a subset of 152 patients. To evaluate the accuracy of the models, the mean absolute error (MAE), root-mean-square error (RMSE) and R-squared were calculated. The best adjusted model was the Ridge Regression with Variable Selection, which obtained the best performance when analyzing both the training group (MAE = 7.54, RMSE = 0.993, R-squared = 0.296) and the evaluation group (MAE = 0.766, RMSE = 1.07, R-squared = 0.282). This tool is still under development, but we have great expectations about its applicability and usefulness for patients who require it.

Keywords: Warfarin; Pharmacogenetics; Dose prediction; Variable selection

Target Prediction and Validation

Interactome of Corynebacterium ulcerans toxigenic strains reveals hub proteins being potential drug targets

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Corynebacterium ulcerans has toxigenic strains that produce the diphtheria toxin similar to C. diphtheriae. Among the bacteria causing diphtheria, C. ulcerans has a greater mutagenic potential because it has both humans and animals as reservoirs. Being reemergent, there was an increase in cases even in immunized countries, requiring new approaches for new drug targets selection. Applying the interolog mapping method we map interactions with confidence score >= 700 from 5090 STRING database organisms, generating the protein-protein interaction network and identifying 22,347 interactions conserved in 10 toxigenic C. ulcerans strains. Selecting by highest degree interaction, 457 hub proteins were identified, 421 (92.12%) of them have the essentiality validated by homology in the Database of Essential Genes (DEG) and 36 (7.88%) were considered essential after functional and enrichment analysis. The Clusters of Orthologous Groups (COG) analysis highlighted the more representative groups: “Translation, ribosomal structure and biogenesis (J)” (74%), “Amino acid transport and metabolism (E)” (13.96%), “Replication, recombination and repair (L)” (8.21%) and only 5.34% “Function Unknown (S)” composed mostly of hypothetical proteins. The Gene Ontology (GO) enrichment analysis identified the most significant biological processes (p>0.95): "Cell redox homeostasis", "DNA recombination", "Cell wall organization", "SOS response", among others. Aiming to select targets do not favoring toxicity, we identified 351 (76.8%) non-host homologous hub proteins, some having higher degree interaction are: “Inosine 5-monophosphate dehydrogenase” (195, CulFRC58_1614), “Protein RecA” (182, recA), “DNA-directed RNA polymerase subunit alpha” (165, rpoA), “2-oxoglutarate dehydrogenase E1 component” (156, odhA) and “DNA-directed RNA polymerase subunit beta” (154, rpoB). All non-host homologous hub proteins possess potential for drug targets and are useful to evaluate the affinity of candidate compounds, experimentally or, similarly that our group performed in-silico affinity test against unpublished synthetic derivatives of tetraisoquinoline alkaloids.

Keywords: bioinformatics; essential proteins; protein-protein interaction

Identification of potential molecular targets related to cancer for the formicamycin's family

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According to the Global Cancer Observatory, 18 million new cases and 9.5 million deaths were estimated for all types of cancer in 2018. The World Health Organization predicts that in 2030 there will be a 70% increase in new cases and 45% in deaths. Due to the rise of cancer incidence and mortality, it is necessary to invest in the discovery and development of new antineoplastic drugs. The novel family of molecules called formicamycin, active against some antibiotic-resistant microorganisms, had a tyrosine kinase enzyme predicted as one of its molecular targets. As this enzyme plays a role in the progression of cancer, the potential antineoplastic action of the formicamycins has been studied. In order to identify the potential molecular targets for an antineoplastic action of the compounds of the formicamycin family, a reverse virtual screening (RVS) was performed using two web servers, PharmMapper and SwissTargetPrediction, to establish the potential targets which interact with them. The targets obtained concomitantly on both servers had their influence on carcinogenesis verified through a literature review in PubMed. The binding energy between target and compound was determined for the targets that seemed to influence carcinogenesis through simulations of molecular docking, with Autodock 4.2 and Autodock Vina, and molecular dynamics, with the GROMACS v.4.6.7 package. Fifteen potential molecular targets were obtained at the intersection of the two RVS servers used. In the literary review, twelve of them were associated with carcinogenesis. These twelve molecular targets were subjected to molecular docking and molecular dynamics simulations. At the end of the RVS process, three potential molecular targets for the formicamycins were identified. Among these macromolecules, nuclear receptor subfamily 1 group I member 2 and matrix metalloproteinase 3 are the most promising targets for an antineoplastic action of these compounds.

Keywords: reverse virtual screening; formicamycin; cancer; bioinformatics

In-silico analysis of the structure and binding site features of the 3cl protease from SARS-CoV-2: parameterization for virtual screening protocols

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The new SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2) emerged at the end of 2019 as a global emergency. Due to its high rate of transmission and the absence of specific treatment or vaccine, around 1 million people over the world have died, according to World Health Organization until October 2020. Nowadays, thousands of people still get infected every day and many of them do not survive due to the complications of the disease associated with the acute respiratory syndrome. Thus, once the pharmacological therapy has shown to be deficient because of its non-specificity, this work intends to conduct an in silico research for possible drugs and bioactive substances, including those belonging to Brazilian biodiversity, that can act as inhibitors of the main viral protease (3CLpro) for the treatment of COVID-19. In this work, the prediction of the amino acid residues' pKa of the receptor protein (PDBid: 6XQT) through the PDB2PQR server and the selection of the ionizable residues' protonation probable state of the 3CLpro three-dimensional structure using the pdb2gmx module were performed as parameterization methods. The anchorage site of the ligands was delimited by the grid center x, y, z: -11, 1, 45 and size x, y, z: 32, 35, 33, respectively, involving the catalytic dyad His41 and Cys145. In the redocking stage, the exhaustiveness of 8, 16, 32, 64 and 100 were tested, with the result of less exhaustiveness being selected with the affinity calculated by Autodock Vina equal to -10.4 kcal/mol. In this step it was possible to obtain an RMSD (Root Mean Square deviation) of 0.97 Å between the original ligand of the crystal and the first model generated from the docking. It was possible to stipulate through the performed methodology the parameters for the next stage of virtual screening, whose results are under analysis.

Keywords: SARS-CoV-2; 3CLpro; drugs

Network pharmacology of annona crassiflora alkaloidal fraction on alzheimer's and its effect on drosophila melanogaster model

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From an alkaloid fraction already identified in a semi-purification of Annona crassiflora previously, a specific enzymatic inhibition was shown. And to harness the full potential of the alkaloid fraction, a network approach was then used. Thus, this work aims to search possible human targets for these alkaloids, and from the targets found evaluate the effect of the alkaloid fraction on the Alzheimer model and predict its pathways of action. Swisstargetprediction and targetnet platforms were used for predicting targets. After the interaction between these targets was predicted with STRING 11.0, the analysis of the interactions to elucidate potential diseases that may be affected was done with DAVID 6.8 platform. All network preparation was done with Cytoscape 3.8.0 software. One of the predicted diseases was Alzheimer's and as cholinesterase inhibitors are currently the main treatment for Alzheimer's, and cholinesterase was a predicted target, I first confirmed that the alkaloid fraction had this activity in an in vitro enzyme assay. With this confirmed, I used the genotype Drosophila melanogaster, which expresses human APP and BACE, generating beta-amyloid, to test the alkaloid fraction by evaluating its motor function intervention with behavioral tests and acetylcholinesterase activity in vivo as well. I observed an improvement in motor behavior and a decrease in acetylcholinesterase activity in vivo and in vitro. After that, we evaluated which other pathways could be affected in drosophila and the impact on Alzheimer's, we made a network with drosophila targets using the DRSC prediction tool - Integrative Ortholog, and with these new networks, we showed other pathways related to Alzheimer's, such as inflammation and oxidative stress. To conclude, these results confirmed acetylcholinesterase as a target and showed a perspective of a potential fraction that can participate in distinct pathways, and then be used for further studies for Alzheimer's.

Keywords: Network Pharmacology; Annonaceae; Alzheimer's Disease; Alkaloid

Virtual Screening

Virtual screening of substances with potential antiviral activity against three flaviviruses: dengue virus, yellow fever virus and zika virus

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Approximately three billion people live in regions at risk of infections by flaviviruses. Dengue virus (DENV), Zika virus (ZIKV) and Yellow fever virus (YFV) presents outbreaks and severe complications. Currently, there are no antivirals available to treat these diseases. We screened and evaluated the potential antiviral activity of small molecules against these viruses, targeting the viral protease NS2B-NS3 (NS3PRO). We used a combination of HQSAR models and structural molecular modelling, based on structures of peptidomimetic DENV-3 NS3PRO inhibitors and molecular docking studies to screen for new compounds. Binding sites of DENV-3 and ZIKV NS3PRO were assessed to build a pharmacophoric model for virtual screening. Hits were selected after molecular dynamics simulations, with predictions of toxicity and biological activity. Biological activities were evaluated by the MTT assay. Antiviral activity was evaluated by plaque reduction, pre-treatment and virucide activity assays. Enzymatic inhibition assays against ZIKV NS3PRO were carried out. An optimal HQSAR model (q2 = 0.67; r2 = 0.87) was selected. A virtual screening of ~7,600,000 compounds was conducted (pharmacophore, docking and molecular dynamics), identifying eight potential inhibitors to the NS3PRO, with favorable biological activity (5/8) and toxicity (8/8) predictions. Five were active against ZIKV, YFV, DENV-2 or DENV-3 (EC50 from 4.21 ± 0.14 to 37.51 ± 0.8 μM, with selective indexes from 1.42 to 3.74), with one being active against all viruses. In plaque reduction assays, two substances reduced about 1.0 to 1.5 log10 of the viral titer of ZIKV, YFV and DENV-2. One also reduced about 1.0 log10 of YFV titer in pre-treatment assays. We have identified five compounds with antiviral activity, with one showing a potential panflavivirus activity. Preliminary ZIKV NS3PRO inhibition assays showed three active compounds with IC50 values between 28 and 69 μM.

Keywords: Antiviral activity; HQSAR; Molecular docking; Molecular dynamics; NS3PRO

Virtual screening suggest potential affinity between *Corynebacterium ulcerans* essential proteins and inedited synthetic derivatives of tetraisoquinoline alkaloids

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Corynebacterium ulcerans is aerobic, gram-positive bacteria that causes diphtheria, by infecting several hosts have a larger reservoir than the other causative agents. Considered reemergent, isolated cases due *C. ulcerans* diphtheria have increased even in immunized nations, highlighting the importance to seek new drugs and treatments. In previous work, we applied the interolog mapping method to generate the interactome, identifying the conserved hub proteins for 10 *C. ulcerans* strains, whose Database of Essential Genes (DEG) validation, COG classification and GO analysis, were confirmed the essentiality of 457 hub proteins, 351 having less than 30% identity against the host, being potential pharmacological targets. Here, we submitted the 351 non-host homologous hub proteins to Phyre2, resulting in 119 viable three-dimensional structure (more than 90% of the amino acids in Ramachandran plot favorable regions). Submitted to fpocket, 145 pockets with drugability score >= 0.5 were identified, which after being subjected to molecular docking in Autodock Vina against a library containing 42 inedited synthetic derivatives of tetraisoquinolinic alkaloid molecules resulted in 6,090 complex, 2,864 getting energy <= -6, considered relevant. The UvrABC system protein B, essential in the DNA repair process, formed the best complex with molecule23 reaching binding energy of -9.9, performing favorable interactions precisely with the protein residues binding to DNA, such as: hydrogen bonds (ARG379, LYS380 and SER166), Van der Waals interactions (ARG146, ASP376, ASP396, GLU122, GLU32, LYS134, MET372 and TYR116), pi-electron interactions (TYR119, TYR119 and TYR169), among others. Additionally, the molecule41 complexed with Bifunctional RNase H/acid phosphatase protein (-9.6); the molecule34 competes for the ADP binding site on Bifunctional protein (-9.5); the molecule20 competes for the uridina-difosfato-n-acetilglicosanima binding site on UDP-N-acetylglucosamine 1-carboxyvinyltransferase protein (-9.4). The results make it possible to understand the molecular binding mechanisms, enabling the rational optimization of molecules, reducing costs associated with synthesis and in-vitro or in-vivo tests.

Keywords: drug target, drug-design, essential proteins; molecular docking; protein-protein interaction

Prediction of protein candidates for drug and vaccine development against pseudomonas aeruginosa infections

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Pseudomonas aeruginosa is a Gram-negative bacterium widely distributed in the environment. As an opportunistic pathogen, P. aeruginosa is associated with high morbidity and mortality in immunocompromised patients worldwide, especially those already affected by cystic fibrosis. Its extensive resistance to antimicrobials and the lack of an effective vaccine leads to an urgency in searching for new therapeutic options. The present work aimed to use the subtractive genomics and reverse vaccinology approaches for the screening of protein targets to develop drug and vaccine against P. aeruginosa. The sequences of 174 complete genomes were retrieved from the NCBI database and processed for the identification of orthologous proteins encoded by all strains using OrthoFinder. The core proteome found to be not homologous to the human host comprised 695 proteins, of which 385 were predicted as cytoplasmic proteins and 310 as proteins exported by P. aeruginosa according to SurfG. We were able to obtain good quality three -dimensional structure models for 71 cytoplasmic proteins using the MHOLline workflow. Among the modeled proteins, 5 best drug target candidates were found using the PBIT pipeline. This selection was made according to the involvement of protein in virulence and essentiality in bacteria, besides the absence of homology with proteins produced by the intestinal microbiota in human. Using Vaxign, 44 candidate antigens were found among the proteins exported by P. aeruginosa, of which 7 presented greater potential for the development of subunit vaccines. Next, the drug target candidates will be used for molecular docking with a library of 5,000 natural plant compounds using AutoDock Vina. Also, immunoinformatic approaches will be considered to select the best antigen epitopes for the formulation of a chimeric subunit vaccine. This work brings up new perspectives to control the highly prevalent and worldwide distributed human P. aeruginosa associated diseases.

Keywords: virtual screening; novel therapeutics; respiratory diseases; protein-ligand docking; bioinformatics

Prospection of protein candidates for drug and vaccine development against *Streptococcus pneumoniae* infections

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Streptococcus pneumoniae is a Gram-positive bacterium and the etiological agent of many diseases related to the respiratory tract (such as pneumonia), meningitis and middle ear infections. The increase in hospitalization rates resulting from pneumococcal infections and the growing reports on antibiotic-resistant pneumococcal strains lead to the development of new prophylactic and treatment methods. In this work, the subtractive genomics and reverse vaccinology approaches were considered to screen protein targets for the development of drug and vaccine against S. pneumoniae infections. The sequences of 63 complete genomes were retrieved from the NCBI database and processed for the identification of orthologous proteins encoded by all strains using OrthoFinder. The core proteome found to be not homologous to Homo sapiens comprised 287 proteins, of which 112 were predicted to be exported by S. pneumoniae and 160 were classified as cytoplasmic proteins by SurfG. As the exported bacterial proteins most likely interact with the host's immune system, we used Vaxign to evaluate the affinity of these proteins for the histocompatibility complex (MHC). This analysis revealed 6 immunogenic proteins with great potential use in subunit vaccine development. In addition, we obtained good quality three-dimensional structure models for 33 cytoplasmic proteins using the MHOLline workflow. Among the modeled proteins, 4 drug target candidates were found using the PBIT pipeline. This selection was made according to the involvement of protein in virulence and essentiality in bacteria, and the absence of homology with proteins present in the human intestinal microbiota. These candidates will be considered for molecular docking with a library of 5,000 natural plant compounds using AutoDock Vina. The present work brings up new perspectives to control the emerging and worldwide distributed *S. pneumoniae* infections in human.

Keywords: pneumococcus; drug target prediction; immunization; bioinformatics

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