CSIR-Open Source Drug Discovery

Annual Report – 2013-14

(www.osdd.net)

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1. Introduction

Working relentlessly in the area of translational research in open source mode, CSIR-Open Source Drug Discovery, in the past seven years, have emerged as the largest open source collaborative effort in drug discovery. Covering all the aspects of drug discovery and development for Neglected Tropical Diseases (NTPs) like Tuberculosis and Malaria, CSIR-OSDD is presently venturing into clinical trials of its new TB drug combination for MDR-TB patients.

OSDD initiative is 11th Five Year Plan project of CSIR, being carried forward through the 12th plan. As the Revised Cost Estimate (RCE) of the project, CSIR-OSDD has been provided an additional funding of Rs 838.00 lakh for the year 2014-15. Hence the total cost of the project as of today stands 5095.500 lakhs till 31st March 2015.

Functioning collaboratively, leveraging on the potentials of crowd sourcing concept, CSIR-OSDD continues to engage scientists and student community across the world to discover and develop drugs for diseases like TB.

2. Some Significant Achievements in the Past Year – 2013-14 : In a Nutshell

Established in 2008, Open Source Drug Discovery (OSDD) Project of CSIR is today a globally benchmarked translational research program and drug discovery platform. A quick overview of some significant achievements of OSDD during the past year is as given below:

Global participation

OSDD today has a global participation of more than 8000 participants from 130 countries across the world. OSDD is partnering with organizations of international repute like Global TB Alliance (GATB, TBAlliance), Drugs for Neglected Diseases Initiative (DNDi), Medicines for Malaria Venture (MMV), Royal Society of Chemistry(RSC) etc. to name a few. OSDD innovation model has been recognized globally.

OSDD has been actively engaged in discussions with World Health Organization towards the development of an open source pharma consortium. OSDD was a recognized participant in the global initiative of Open Source Pharma called "*Towards New Open Pharmaceutical Industry*" held in July 2014 at the Rockefeller Foundation Bellagio Center, Italy. The first of it's kind, international conference aimed at developing a global, open source pharma ecosystem, the goal of the meeting was to launch concrete new initiatives to discover, develop, and commercialize medicines for the most pressing needs in our society through the use of open and inclusive research models.

Clinical Trials of New TB Drug combination for MDR-TB Patients

In March 2014, OSDD obtained the approval of Drug Controller General of India for conducting Phase II B clinical trials for the new combination regimen for MDR-TB. This new combination regimen is being taken up by TB Alliance, USA in other parts of the world. The trial will be conducted at National Institute of Tuberculosis & Respiratory Diseases (NITRD), New Delhi. The final protocol for this trial was released by Dr T Ramasami, at NITRD on the occasion of World TB Day on 24th March 2014.

This will be a3 arm study-In the first arm patients will be treated with a combination of PA 824, Moxifloxacin and Pyrazinamide (PaMZ), in thesecond arm of PA-824 will be added to the current Standard of Care (DOTS PLUS) and the thirdwill consist of the Standard of Care. Institutes likeNational Institute for Research in Tuberculosis (NIRT), Chennai and CROs like M/s G V K Biosciences are also involved in the trial. Approval fromEthics Committeeof NITRD and RNTCP board have also been obtained. The import license for PA-824 has also been obtained and the drug entity is repackaged and is ready for the study.On successfully completing all stages of clinical trials, this new drug combination will be made available at an affordable cost without any royalty to the needy patients in the country.

TATA-CSIR-OSDD Fellowship for Students

In recognition of the work done by OSDD students, Sir Dorabji Tata Trust in October 2013 awarded a Grant to enable Council of Scientific & Industrial Research (CSIR), New Delhi for operating TATA CSIR-OSDD Fellowship (TCOF) to support students and young researchers who will participate in the process of "crowd sourcing" as a method of research on open source discovery of drugs for neglected diseases like Tuberculosis (TB) and Malaria. The Grant amounts to Rs.285.75 lakhs for a period of 3 years. A project proposal was submitted to Sir Dorabji TATA Trust for a joint TATA CSIR-OSDD fellowship grant in early 2013. Upon sanction, a strategy for disbursal was streamlined based on invited comments through Sysborg 2.0 portal *(http://sysborg2.osdd.net)* and OSDD website *(www.osdd.net).* As per the guidelines, Project Director, OSDD nominated two committees for assessing applications for the three fellowship schemes, namely, i) TCOF (TATA CSIR-OSDD Fellowship), ii) TCOS (TATA CSIR-OSDD Scholarship) and iii) TCOWF(TATA CSIR-OSDD Women Fellowship). The committees (One jointly for TCOF & TCOS, another for TCOWF), headed by a convener, are responsible for checking the scientific credibility of the submitted project, eligibility of the candidate and assessing the alignment of the work with the overall objectives of OSDD. The entire effort is coordinated by the TATA Fellowships Coordination Cell based at CSIR-OSDD Research Unit, IISc, Bangalore.

The objective of this fellowship is to train a large number of researchers / students on drug discovery related scientific areas through the work of Open Source Drug Discovery (OSDD) for neglected diseases. The fellowship is given to researchers who may or may not be currently students – such as for example the

women scientists who are working from home, independent researchers who may be post-doctoral and doctoral fellows or even post graduates with excellent track record.

The fellowship is now enabling students, especially women, across the country to undertake research and contribute towards the OSDD vision of providing affordable healthcare.

OSDD Drug Discovery Programs and Platform

With an aim to accelerate the discovery of new drugs to TB, OSDD is pursuing several drug discovery projects in collaboration with various academic scientists and institutions .Realizing the urgent need for diverse small molecule chemical libraries, OSDD has initiated several chemistry projects involving about 90 PIs from many CSIR labs like IICT, NCL, NIEST, NIIST, CLRI, CDRI and IIIM. The compounds synthesized by the scientists are stored in a central repository at National MOL Bank at IICT. About 10,000 compounds have been screened against Mycobacteria (at IICT and CRO Premas Biotech) and 12 primary actives are being pursued further for optimization. In addition, Hit optimization and SAR studies are in progress with Jubilant Chemsys.

Various chemists from various Universities, Institutes and Colleges are involved in synthesis of compounds via OSDDChem - an open access chemical repository. These compounds are being screened against TB and Malaria at CDRI.

Apart from the whole cell based screening, target based screening is also underway at various labs (IGIB, NII, University of Hyderabad, IICT, NIIST, BITS-Hyderabad and others) and at CRO Anthem Biosciences. Biochemical and genetic validation of Drug targets at experimental level predicted from systems level analysis of Mtb are being pursued. Several novel approaches to target Mtb are also underway.

With these efforts OSDD has built a translational platform to convert the valuable scientific findings into drug discovery projects and has built a portfolio of early drug discovery projects.

OSDD has build up a host of open source facilities aiming to equip the researchers with easily accessible resources to enable their research. These facilities include:

- Open Source Chemical Repository – OSDDChem at CDRI
- Open Screening Facility at IICT
- Free Access Computational Resources- OSDD Community has developed a package known as Computational Resources for Drug Discovery – an open in silico module for drug discovery which contain many resources like Tbrowse , KiDoq, ccPDB, IPW, GiDoQ, MetaPred, KetoDrug, CRDD etc.

The community has also developed OSDDlinux - a customized linux operating system for drug discovery that integrates open source software, libraries, workflows and web services in linux for creating environment for drug discovery.

Connect to Decode Phase II and Building a Systems Biology Platform

Following the success of Phase I of Connect to Decode (C2D) program that successfully adopted Crowd sourcing approach to genome scale re-annotation of *Mycobacterium tuberculosis* for identification of novel drug targets, OSDD undertook Phase II of C2D. During this phase, large scale computing projects and distributed community collaborative projects were successfully completed. The Open Source Chemistry Initiative under phase II resulted in the creation of OSDDChem-the open chemical repository along with development of a Cheminformatics community. The community with 400 registered members seeks to address the challenge of identifying molecules available in large online digital repositories with desired set of drug like properties, using computational tools. The project concentrated on the use of chemical descriptors and data mining approaches to discover and mine novel molecules with desirable properties and data curation and integration of chemical data along with annotation from various data sources in standardized formats. The group successfully developed predictive models for in-vitro anti tubercular activity and toxicity of molecules. Under this phase the OSDD community has also developed platforms and databases for curating and analyses of potential hits with most recent being the resource on phytomolecules (http://crdd.osdd.net/servers/biophytmol/) to identify chemical compounds with anti-tubercular activity from plants.

Building a Systems Biology Platform with the objective of gaining in-depth understanding of Mycobacterium tuberculosis, a Systems Biology Spindle Map (SBSM)' of metabolism that enables the visualization of metabolic data of Mtb has also been designed. Systems Biology Spindle Map helps in simulating and visualizing the entire metabolic process of Mtb in terms of its genes, metabolites, enzyme catalysts and reactions to evaluate potential drug targets.

3. Activities going on in various CSIR labs under OSDD umbrella – Meeting with DG, CSIR

CSIR-OSDD works on the principle of crowd –sourcing and distributed co-creation. Adhering to this, CSIR-OSDD has developed an extensive network of collaborations involving CSIR laboratories as well as other academic and R & D institutions worldwide.

Some of the major CSIR laboratories currently involved in OSDD activities are as follows:

1. CSIR-Central Drug Research Institute (CDRI), Lucknow
2. CSIR-Institute of Genomics and Integrative Biology (IGIB), Delhi
3. CSIR-Indian Institute of Chemical Biology (IICB), Kolkata
4. CSIR-Indian Institute of Chemical Technology (IICT), Hyderabad
5. CSIR-Indian Institute of Integrative Medicine (IIIM), Jammu
6. CSIR-Institute of Microbial Technology (IMTECH), Chandigarh
7. CSIR-National Chemical Laboratory (NCL), Pune
8. CSIR-North East Institute of Science and Technology (NEIST), Jorhat
9. CSIR-National Institute for Interdisciplinary Science and Technology (NIIST), Trivandrum

In order to understand the involvement of CSIR institutes in the ongoing work with CSIR-OSDD and their commitments with OSDD unit a meeting with the concerned Principle Investigators from the CSIR laboratories along with members of CSIR-OSDD unit and Director General, CSIR was conducted on 07.08 2014 in New Delhi. A total of 40 researchers from the above mentioned 9 laboratories participated in the meeting. The representatives from various CSIR institutes made brief presentations highlighting the activities being conducted in their institute under the OSDD umbrella.

Brief Work Reports

Participants from CSIR-HQ

1. Dr. P.S.Ahuja (DG CSIR)
2. Dr. Sudeep Kumar (CSIR-PPD)
3. Dr. T.S. Balganesh (CSIR-OSDD)
4. Dr. Sarala Balachandran (CSIR-OSDD)
5. Dr. Geetha Vani Rayasam (CSIR-OSDD)
6. Dr. Swati Subodh (CSIR-OSDD)
7. Dr. Anshu Bhardwaj (CSIR-OSDD)

CSIR-Central Drug Research Institute (CDRI), Lucknow

The following researchers from CSIR-CDRI participated in the meeting:

Dr. S.K. Puri
Dr. Saman Habib
Dr. Sanjay Batra

Dr. K.K. Srivastava
Dr. Niti Kumar
Dr. Sidharth Chopra

The CSIR-CDRI team is involved in the operation of OSDD's open chemical repository –OSDDChem. CSIR-CDRI has undertaken some initial screening against TB (M. Habana H37Ra) and Malaria (P. falciparum (3D&, CQS) which has yielded a few hits. It was appraise during the meeting that the ground work in the area of malaria to initiate OSDDm had been laid but the project could not be pursued further due to lack of funds. The possibility of development and adoption of innovative screening methods was discussed during the presentation.

CSIR-Institute of Genomics and Integrative Biology (IGIB), Delhi

The following researchers from CSIR-IGIB participated in the meeting:

Dr. Rajesh S. Gokhale
Dr. S. Ramachandran

CSIR-IGIB has been involved in target based drug discovery involving multi target (FAALS & FACL) based approach. CSIR-IGIB has made significant Contributions towards setting up of Syborg 2.0 portal and implementing Connect2Decode project. The ongoing work at CSIR-IGIB under the OSDD umbrella includes target based screening of DapA inhibitors, creating a comprehensive Systems Biology model of Mtb and Pharmacogenomics aspects of Anti-TB drugs. .

CSIR-Indian Institute of Chemical Biology (IICB), Kolkata

Researchers of CSIR-IICB are involved in both developmental activities using informatics tools as well as discovery through synthesis of novel compounds of interest against TB. The possibility of futhering studies on *Imipramine* as an Anti-Leishmanial candidate was discussed during the meeting.

CSIR-Indian Institute of Chemical Technology (IICT), Hyderabad

The following researchers from CSIR-IICT participated in the meeting:

Dr. G. Narahari Sastry
Dr. Haridas Rode

Dr. Prathama Mainkar
Dr. Ramesh Ummani

CSIR-IICT is involved in extensive synthesis of novel molecules involving around 25 PIs. CSIR-IICT hosts the central repository called MOL Bank to store the novel compounds synthesized by the scientists. The compounds are being screened against *M. smegmatis*. Cytotoxicity studies of hits are also being undertaken the laboratory. CSIR-IICT is one of the key participants in the development of Molecular Property Diagnostic Suites (MPDS).

CSIR-Indian Institute of Integrative Medicine (IIIM), Jammu

The following researchers from CSIR-IIIM participated in the meeting:

Dr. Ram A. Vishwakarma
Dr. Inshad Ali Khan
Dr. Parvinder Pal Singh

CSIR-IIIM is maintaining a natural products repository and is actively involved in screening of synthetic compounds. CSIR-IIIM has established a large open screening facility and has obtained few hits against TB. The institution is involved in lead optimizations and pre-clinical validation of some of the compounds. The ongoing work involves putative multidrug resistant efflux pump inhibitors.

CSIR-Institute of Microbial Technology (IMTech), Chandigarh

Dr. G.P.S.Raghava from CSIR-IMTech participated in the meeting

CSIR-IMtech has been actively contributing towards the development of open source computational tools for drug discovery and development under the Computational Resources for Drug Discovery (CRDD) module of OSDD. Recently, CSIR-IMtech has been involved in the development of OSDDlinux - a customized Linux based platform for drug discovery. Like CSIR-IICT, CSIR-IMTech is also a key participant in the development of Molecular Property Diagnostic Suites (MPDS).

CSIR-National Chemical Laboratory (NCL), Pune

The following researchers from CSIR-NCL participated in the meeting:

Dr. Sourav Pal

Dr. C.V. Ramana
Dr. Sanjib Gogoi
Dr. Pradeep Kumar Tripathi
Dr. Akkattu T. Biju
Dr. Srinivasa Reddy D.
Dr. Santosh B. Mhaske
Dr. Subhash Prataprao Chavan
Dr. M. Muthukrishnan
Dr. Dhiman Sarkar
Dr. Vandana Pore
Dr. Muthukumarasamy Karthikeyan
Dr. H Borate
Dr Jayant Gajbhiye

CSIR-NCL is involved in the chemical synthesis of potential drug-like candidates against TB. Under this initiative a number of compounds have been synthesized and submitted for assaying anti-TB activity. Besides this CSIR-NCL is also involved in extensive Outreach program, under which students are provided training in the areas of chemical synthesis and drug discovery. CSIR-NCL is also involved in the development of Molecular Property Diagnostic Suites (MPDS).Working in close collaboration with the Royal Society of Chemistry in organizing Open Challenges. The researchers of the institute are working on target based inhibitor synthesis for MMpL3 in Mtb.

CSIR-North East Institute of Science and Technology (NEIST), Jorhat

The following researchers from CSIR-NEIST participated in the meeting

Dr. Anil Singh
Dr. Pranjal Gogoi
Dr. Pallab Pahari

CSIR-NEIST has synthesized several new compounds of interest against TB that has been screened in-house as well as sent for screening at Mol Bank. The main focus is on obtaining natural products and synthesis of novel compounds with better activity against TB.

CSIR-National Institute for Interdisciplinary Science and Technology (NIIST), Trivandrum

The following researchers from CSIR-NIIST participated in the meeting

Dr. Managalam Nair
Dr. K. MadhavanNampoothiri

CSIR-NIIST is focused on diversity oriented synthesis to arrive at compounds with potent activity against Mtb. Under this effort researchers of CSIR-NIIST are involved in the synthesis of new chemical entities from benzoyl fumarates. The institute is also involved in expression and purification of methionine peptidase enzyme from Mtb in order to screen compounds against the same. CSIR-NIIST is also involved in extensive Outreach program, under which students are provided training in the areas of chemical synthesis and drug discovery.

4. Funding Status of CSIR-OSDD

The core funding of OSDD is from the Government of India. For the period of September 2008 to March 2012 under the 11th Five Year Plan (FYP)Government of India had earmarked Rs 45.97 crores for the project. Up to 2012 OSDD was a project under National Laboratories Scheme of CSIR. For the 12th five-year plan during 2013-2017, the planning commission has approved the continuation of OSDD as a part of Scheme for Open Innovation of CSIR. The EFC for OSDD project for the 12th FYP has been completed. In the interim period as the Revised Cost Estimate (RCE) of the project, CSIR-OSDD has been provided an additional funding of Rs 838.00 lakh for the year 2014-15. Hence the total cost of the project as of today stands 5095.500 lakhs till 31st March 2015. The Cabinet note for the sanction of 150 crores for the remaining period in the 12th FYP is in the final stages.

In addition, Sir Dorabji Tata Trust has awarded a Grant to enable CSIR for operating TATA CSIR-OSDD Fellowship (TCOF) to support students and young researchers who will participate in the process of “crowd sourcing” as a method of research on open source discovery of drugs for neglected diseases like Tuberculosis (TB) and Malaria. The Grant amounts to Rs.285.75 lakhs for a period of 3 years. The first installment of Rs. 95.25 Lakhs has been received at CSIR.

5. OSDD Scientific Activities – Current Status in Detail

a) Predictive Sciences

Breaking way from the traditional hit and trial methods of drug discovery, OSDD leverages largely on the strength of computational and predictive sciences to create a dynamic and robust drug discovery pipeline. During 2013-14 OSDD has taken up three large initiatives in this context namely the development of Molecular Property Diagnostic Suite and OSDDChemDesign and hosting of OSDD's open research portal Sysborg 2.0 from NIC/NKN Datacenter. The detailed report on these activities is as follows.

Molecular Property Diagnostic Suite (MPDS):

Participants: OSDD Unit (Delhi), NIPER (Mohali), IICT (Hyderabad), CLRI (Chennai), JNU (Delhi), NCL (Pune)

The objective of the MPDS suite is to establish an integrated drug discovery pipeline for OSDD. The first phase was to establish the workflow system with open source tools available in public domain and those developed in the labs of the participating PIs. The ultimate goal is to assess and estimate the property of a given molecule using chemoinformatics tools in order to diagnose their potential application as drug. As of now the following databases and tools are integrated into the workflow system:

1. Databases: PubChem, DrugBank, ZINC, Asinex, KEGG, NCI, Mtb Target Library
2. Tools: Docking (autodock/autodock vina), ligplot, JMOL, JME, CDK, PADEL, DruLiTo, QSAR, WEKA, CIRCOS

In order to do so all the databases and tools were first converted into XML standard for Galaxy. These XML were then tested and used to generate workflows. As most of the team members were new to Workflow systems, a workshop was organized at CMMACS, Bangalore, in July 2013 to train the team and also integrate the publicly available resources into Galaxy. Subsequently, two more workshops were planned in September 2013 at IICT and January 2014 at NCL. The plan and the progress made during the workshops may be seen at

http://sysborg2.osdd.net/group/sysborgtb/lab-notebookdetails?p_p_id=project_WAR_projectportlet&p_p_lifecycle=1&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_project_WAR_projectportlet_resourcePrimKey=6211&_project_WAR_projectportlet_javax.portlet.action=showLabnotebook

The ver1.0.1 of MPDS portal has the following nine modules:

1. Target library (~150 drug targets of Mtb)
2. Compound library (~57 Million compounds fingerprinted)
3. Fragment library
4. Docking module
5. QSAR module
6. Drug like filters module
7. Descriptor calculator module
8. Visualization
9. File format converters

A beta version of the MPDS platform may be accessed at http://mpds.stage.osdd.net/

OSDDChemDesign: A platform for Compound Submission for Biological Screening

OSDDChemDesign is a web-based platform providing access to the compounds synthesized and screened by the OSDD Community along with details on compound structures, physiochemical properties, etc. In addition to chemical data, the platform is also customized to capture biological screening data, which includes whole cell based assays (M. smegmatis and M. tuberculosis), target based assay and cytotoxicity assays. For each assay performed, an assay ID has been assigned. The Community can provide additional assays, if they have followed a different protocol for screening and in such cases new assay IDs will be generated. The entire data in OSDDChemDesign may be browsed for Identifiers, Classification Data, Biological Screening, Physicochemical Properties, Data Source, Record with Full Details. OSDD has a strong team of synthetic and medicinal chemists pan India. Over past two years, the OSDD Chemistry Community has synthesized a large number of compounds. These compounds are designed with the objective of identifying novel scaffolds with anti-TB properties. It was imperative to set up a synthesis-screening system that facilitates the understanding of biological activity of these synthesized compounds to identify potential hits and iteratively enhance their efficacy and drug-like properties. As of now, more than 80 synthetic chemists are involved in synthesis of different classes of chemical compounds. These efforts are complemented by different screening platforms both in academia and as services from CROs, which are set up as open screening facility by OSDD. The synthesis of compounds as well as screening takes places across several geographically distributed locations. Therefore, it is essential to set up a central repository for storing of compounds, the information associated with these compounds along with biological screening data.

Currently ~5000 compounds and associated biological screening data have been deposited in the OSDD ChemDesign database and may be accessed at: http://crdd.osdd.net/servers/osddchemdesign/

Sysborg hosted from NIC/NKN Datacenter

SysBorg Portal http://sysborg2.osdd.net is now hosted at the NIC/NKN Data center with a new architecture to ensure continuous access. The OSDD Community is welcome to test the new system and report any bugs or issues to info@osdd.net. New features have been incorporated making the system user-friendly.

b) Cheminformatics

1) Developed Cheminformatics Model for Prediction of Non-Drug Discovery Related Experimental Results like Semi-conductor Activity

   "Computational Predictive Models for Organic Semiconductors, Journal of Computational Electronics (Springer US) December 2013, Volume 12, Issue 4, pp 790-795,Date: 13 Jul 2013. R. Sajeev, R. S. Athira, M. Nufail, K. R. Jinu Raj, M. Rakhila, Sreejith M. Nair, Andrew Titus Manuel , U. C. Abdul Jaleel.

2) Datamining models by using Random Forest and Bayesian statistics were developed and screened the molecules from the open chemical space and published works in open blogs. Two papers were communicated for publications in Medicinal Chemistry Research and Journal of Chemical Information and Modeling.

3) For the validation of Structure Based tools experimentally obtained toxicity results were used and these results were published in "Applied Toxicology and Molecular Similarity".

4) Since experimentally active molecules are available in open space for different diseases, prioritizing such molecules for synthesis and in vitro screening may produce some hits. That can be further optimized by Medicinal Chemistry approach.

   (a) Development of MedChem Promiscuity prediction server, Status: Finished phase one open for public [OSDD MPDS project]

High throughput screening often gives false output, usually because of compounds that are unstable, promiscuous nature, toxicity and interfering with assay measurements. A server will be set up which can be used to assess and predict the promiscuous compounds from large databases to control the rate of attrition during clinical study.

(b) Creation of integrated cross-platform Cheminformatics software with Avogadro and Autodock. (TCOWF2) , Status: Finished

(c) Implementation of Random Forest Classifier on CUDA for virtual drug design with necessary optimizations (Collaborative work with TCOF 1), Status : Finished opened for public

Of all machine learning classification algorithms, random forest appears to produce more significant results in medicinal chemistry. The reason behind this can be attributed to random feature selection and repeated feature evaluation. Random forests are a collection of decision trees, that are initially trained with examples and appropriate weights are assigned to each descriptor. The sparse nature of biological data can be taken to advantage and the existing random forest algorithm can be modified. By developing a GPU-based algorithm, the enormous computing power of GPU can be used on large data sets. The aim of this project was to develop a GPU based random forest classifier for virtual screening that represents and considers all the descriptors.

(d) Repositioning different chemical classes for Anti-TB virtual screening. (TCOF 3), Status: On-going

Today's scenario is more of a Chemo-centric led ligand based approach aided by Artificial Intelligence (AI), as it has been gaining importance steadily in the drug discovery process. This approach is based on the hypothesis of using the chemical similarity among ligand sets as a representation for the pharmacological similarities of the protein targets and hence would quantify target similarity on the basis of similarities of ligands.

(e) Virtual Screening of the Inconclusive Data of PubChem Bioassays (TCOS 2 project), Status: Finished phase 1 [Article: communicated]

5) Following papers were communicated which was an outcome of crowd sourcing activities under the leadership of DrJaleel as the PI of the project.

(a) "Virtual Screening and Repositioning of Inconclusive Molecules of Beta-lactamase Bioassays-A Data Mining Approach" submitted to Medicinal Chemistry Research.
(b) LJAJUC papers

6) Took forward the GSK molecules as planned for prioritizing some molecules/ open source molecules/ CDD molecules that are specific target based and ligand based hits

c) <u>Library Building and Hit Identification Programs</u>

OSDD has undertaken an initiative to work with scientists across various CSIR Labs and other institutions to build a diverse compound library that would be screened for TB and Malaria.Towards this objective the various CSIR chemistry labs are involved in design and synthesis of compounds that are centrally stored at National Mol Bank at CSIR-IICT. They are initially screened on *M smegmatis* at IICT and further validated in *M.tb* by OSDD. The number of compounds from each Institute is proportional to the number of Scientists involved in this activity. The summary of the ongoing activities is described below.

1. CSIR-IICT

CSIR-IICT scientists have been contributing actively to the OSDD diverse compound library synthesis. Total 25 scientists are involved and 1200 compounds have been synthesized. These compounds are stored in the National Mol Bank and are screening against *M semgmatis* at IICT. The 'hits' from this are then screened against *M. tb.* at a CRO. Several hits active in *M.tb.* have been identified so far.

2. CSIR-NEIST

CSIR-NEIST team involving 5 researchers have delivered 43 new synthetic molecules among which almost 6 molecules are showing preliminary activity against TB. Also the biological team has been isolated around 30 active microbial strains by screening them against non-tubercular mycobacterial strains (NTM).

For isolation of diverse range of bacteria, the soil samples were collected different untapped region of northeast India. More than 1500 bacteria have been isolated from different soil and water samples collected from different part of northeast region and the work is still in progress. More than 1200 bacterial isolates have been screened against two mycobacteria strains (*Mycobacterium smegmatis* and *Mycobacterium abscessus*). As a result, there are total 23 bacterial isolates from various locations that are showing good activity against both the mycobacterial strains**..** Isolation of active metabolites from these effective isolates has been currently going on. Few are looking promising that will be submitted for MTB screening very soon.

3. CSIR-NCL

14 scientists from CSIR-NCL are actively participating in this program. Synthesis of a focused collection of small molecules around the hits that have been identified during the preliminary screening for lead optimization and profiling in ADMET assays. These include like derivatives of thienopyrimidine, further optimization of the two series designed around BM212 scaffold (Sila analogues of pyrrole & Sila analogues pyrazole). Some of the initial hits with promising anti-TB potential (sub-micro molar MIC values MIC ~ *40 nanomolar*) and good selectivity index will be further optimized for the planned animal experiments. Total of 647 compounds have been submitted to CSIR-IICT Mol Bank. 15 students have been trained under OSDD

project. Currently synthesis of compounds is underway. It is proposed to synthesize around 200 compounds and train around 10 students under OSDD activities.

4. CSIR-NIIST

As part of the on-going OSDD programme, during 2012-2014, four NIIST scientists have prepared around 130 compounds and the preliminary screening studies of selected molecules at OSDD center showed that some of the compounds are found to be active against tuberculosis. Several efficient methodologies have been developed for the construction of a variety of biologically relevant carbocyclic and heterocyclic scaffolds. They were successful in generating libraries of compound classes including cyclopentene fused chromanones, pyrazolidine-benzofuran fused cyclopentenes, indoline-pyrazolidine fused cyclopentenes,functionalized spiro[2.4]heptenes, alkylidenecyclopentenes, spiro-oxindoles, isoquinolone fused azabicycles, mono- and biscyclopentenyl functionalized aza-heteroaromatics,substituted trienes*etc*. During the same period, isolation, synthetic modifications and biological studies of natural products have been carried out.

d) OSDDChem Outreach at CSIR-CDRI

Activities under OSDD Chemistry Outreach were continued in the year 2013-2014. During the period a total of 307 compounds from different projects sanctioned under the OSDD Chem outreach program were received at CSIR-CDRI for screening. From this 257 compounds were taken up for evaluation as ant tubercular or antimalarial or for both bioactivities. A total of 218 compounds were screened as antimalarials whereas 103 compounds were screened for their anti tubercular activity. Beside in house synthesis of certain chemical starting points suggested by Medicines for Malaria Venture was initiated. More than 20 analogues from different series were synthesized and assessed for their antimalarial activity

e) Whole cell Screening Activities

Screening at IICT

At present NMB has a repository of ~12000 compounds which are being screened against *Mycobacterium smegmatis* and *M.bovis* at CSIR-IICT. The procurement of small molecules is a continuous process and the library will be expanded as time progresses. CSIR-IICT Biology team has established dedicated screening facility with *Mycobacterium smegmatis* to evaluate compounds coming into NMB. As part the currently on going OSDD project, all the 12,000 compounds have been screened against *M smegmatis* at 30uM concentration. Currently about 350 primary hits were identified from NMB library showing anti mycobacterial activity. In addition to screening on *M smegmatis*, the 'hit' compounds are also tested for cytotoxicity on

mammalian cell lines such as A549 and HepG2 at IICT. Recently, screening on *M. bovis* (BCG) has been set up at IICT and will be used going forward for the screening of compounds in MOL Bank.

Screening at CRO on *M.tb.*

While *M smegmatis* or BCG, are convenient for initial screening they are only surrogate models. The compounds need to be effective on M tb. As *Mtb* needs to be cultured in BSL3 conditions and also screening of large number of compounds in an SOP driven manner is required a CRO has been hired by OSDD for this purpose. Those compounds that show 40% inhibition at IICT upon screening at *M semgmatis* were tested against Mtb at Premas Biotech. The compounds are initially tested at single conc. of 30uM on Mtb. So far about 450 compounds have been screened at a single conc. of 30uM. Compounds are that are sensitive to the Mtb at 30uM are then tested for MIC. 175 compounds were tested for MIC and several compounds have been identified that have potent MICs. OSDD has confirmed 120 potential molecules with antitubercular activity. The way forward is to synthesize analogs around each scaffold identified to further progress towards identifying new leads from hits to obtain new anti-tubercular agents.

In addition, to these about 200, CDRI 830 analogs synthesized by Jubilant were tested at Premas Biotech for MICs.

Screening of Plant Extracts on Mtb: About 1000 enriched fractions from plants (obtained from Phytomyco) were screened against Mtb at a single concentration at Premas Biotech. 7 samples have shown anti TB activity and validation is in progress.

f) Assay Development and Target Based Screening at CRO

OSDD is working with Anthem Biosciences, a CRO with molecular biology and biochemistry expertise, to develop and perform target-based screening campaigns with the OSDD molecule library (MolBank). Currently Anthem is working with two targets that are being studied as part of the OSDD portfolio; DapA/DapB and FadDenzymes.

DapA/B Target: The low-throughput assay for DapA and DapB pair of enzymes was initially developed by Dr. Ramachandran at IGIB, optimized by Enzene, another CRO, and then transferred to Anthem for high-throughput screening. In the last year this assay was screened with ~3500 compounds from the MolBank library at 10 uM in duplicate. In this primary screen 227 compounds showed an average of 40% inhibition and were therefore tested for dose-response activity. The activity of several compounds were confirmed and showed dose response activity, of which 37 compounds showed 50% inhibitory activity at 50 uM or less. These 37 compounds were re-tested for dose-response activity to confirm the IC50 and a final set of 15 compounds are now being evaluated as validated hits from the screen. Their activity will be reconfirmed in a

low-throughput assay from a fresh supply of the compound from MolBank followed by structure-activity relationship studies of prioritized hits.

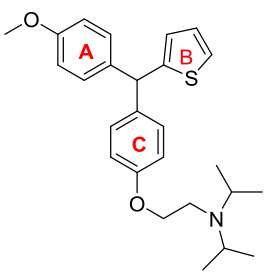
FAACL/FAALs: With OSDD, Dr. Rajesh Gokhale and his team of scientists at CSIR-IGIB have been actively involved in demonstrating the function of fatty acid activating enzymes called FadDs (comprised of two forms; FACLs and FAALs) and have utilized the strategy of targeting both forms with a single inhibitor. OSDD has engaged with Anthem to help develop a robust non-radioactive assay that can assess the enzyme activity of both FAALs and FACLs. This would provide valuable assessments of the structure-activity relationship of new compounds designed to target both forms of the FadDs. In addition, a robust non-radioactive assay would afford the possibility of screening a diverse compound library for new scaffolds with similar mult-target activity. OSDD has co-ordinated the transfer of materials and protocols for the expression and purification of several FadD enzymes from Dr. Gokhale's laboratory to Anthem. Anthem then optimized the protein expression and purification conditions for four of these proteins. They have performed preliminary tests with a non-radioactive assay and shown that they can detect the enzyme activity of both FAALs and FACLs. They are now using one target protein, FAAL32, to further optimize the biochemistry and develop an assay that can be used for testing previously designed FadD inhibitors as well as for larger library screening.

g) Hit Optimization Program

CDRI-830

A lead compound CDRI830 showing anti-Mtb activity was discovered via a whole cell screening of a library of compounds at Central Drug Research Institute Lucknow

(Preclinical development of Thiophene containing trisubstituted methanes; Dr Gautam Panda and Dr Sudhir Sinha, CSIR-CDRI)



Initial SAR studies conducted at CDRI by synthesizing >150close analogs of the lead compound indicated a narrow SAR for whole cell activity. The critical pharmacophore fragment is a triaryl methane with dialkylaminoalkyl ether in one of the phenyl rings (preferably in ring C). The ring A tolerates alkoxy, alkylthio and halogen groups in *p* and *m* positions whereas, the thiophene ring could be replaced with pyridyl, indolyl, pyrrolylor a naphthyl ring, albeit with some loss of potency. It is obvious from the CDRI data that diisoprpylamino side chain attached to ring C is critical because other substituents were either less effective or completely devoid of any measurable antibacterial activity. However, the parent molecule, CDRI-830 was shown to have efficacy in an animal model of Mtb and its effectiveness was synergistic with other front line Tb therapies like Isoniazid and rifampicin. It was also found to be non-toxic in a cytotoxicity assay.

OSDD ASSESMENT:

Strength:

1. Active against Mtb
2. Lead-like molecule- MW <500, PK and efficacy demonstrated, and chemical opportunities to expand the molecule to build potency and properties, etc.
3. Initial SAR available - Near neighbors with moderate to potent MICs
4. Good chemical tractability – synthetic routes enabling rapid analog synthesis

Weaknesses:

1. CDRI-830 has a chiral center – compounds made and tested were all racemic mixtures.
2. High cLogP (6.9) and hence poor aqueous solubility
3. Low polar surface area (<30 SqÅ)
4. Limited SAR (SAR needs expansion to establish pharmacophoreandtoxicophore, improve physicochemical properties)
5. Limited toxicity data
6. Triarylmethane system– known to have a wide variety of biological activities
7. More than 1 aromatic ring linked to a tertiary amine via an alkyl or alkoxy chain functionality with high pKa value (>8) and high cLogP (>5)– features known to bind to neuronal receptors as well as inhibit hERG channel.

Taking into account that the molecule had already shown efficacy an appropriate animal model, the safety liabilities of the molecule were investigated against a panel of receptors and kinases. These studies were conducted at Cerep, Le Bios l'Eveque in France. Study results indicated that CDRI-830 did not significantly inhibit any of the kinase enzymes. However, it was found to potently inhibit the binding of the native ligand to

bind to four receptors:M2 (Muscarinic receptor), 5H2, norepinephrine and dopamine transporters between 65-95% at 10 µM concentration. Furthermore CDRI-830 was further tested at Advinus Therapeutics Limited in Bangalore, India for its potential to inhibit hERG channels. Results indicated that at 30 µM concentration CDRI-830 showed about 66% inhibition of the hERG channel.

The med chem design of the series was made taking all of the above information into account.

Optimization of objectives for CDRI-830:

1. Improve potency to MIC < 5 µM.
2. Expand SAR and SPR to establish a pharmacophore and toxicophore while focusing on improving potency (MIC <5µM) and addressing the tox issues
3. Resolve CDRI-830 into its enantiomers, test them for MIC to see if there is a selectivity
4. Establish safety issues: Test CDRI-830 for selectivity – test it against a panel of kinase enzymes and also for its binding to CNS receptors, hERG channel, etc.

Interpretation of tox results and medicinal chemistry plans:

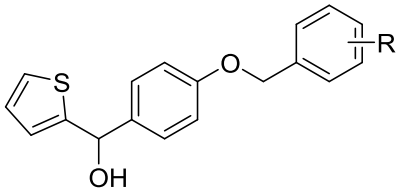
Strong binding to CNS receptors and inhibition of hERG channel by CDRI-830 are critical issues to addressed in designing the work plan. Binding to CNS receptors and inhibition of hERG channel are characteristic of compounds that have a combination of high lipophilicity (cLogP>5), more than one aromatic ring, a tertiary-amine linker and an overall pKa of >8. These properties of CDRI-830 are, cLogP = 6.9, three aromatic rings with a diisopropyl-amine sidechain, and a calculated pKa of 9.7. Our hypothesis of structurally linking CDRI-830 to the observed binding to various receptors is supported by the literature on dopamine receptor agonists as well as FDA approved dopamine receptor agonists, antihistamines (H1 receptor antagonists), etc. Therefore we envisioned that bringing down both LogP and pKa properties of CDRI-830 through structural modifications should significantly reduce its binding to CNS receptors as well inhibition of the hERG channel.

It was anticipated that in this process of addressing tox issues, the intended modifications would also help build a strong SAR, establish a pharmacophore and improve the potency to the targeted level. A contract was set up with Jubilant Chemsys in Noida to synthesize molecules designed by the OSDD medicinal chemistry team. The synthesis work began in March 2013 with 4 synthetic chemists on board. Desired structures, compound quality requirements and submission protocols were established by the OSDD team. Furthermore, OSDD continuously guided and monitored synthesis activities to insure intended progress.In addition, inputs into the program and some of the synthesis was carried out by DrGautam Panda at CDRI

Accomplishments:

- Designed CDRI-830 analogs with the view to understand the pharmacophore, keeping the calculated properties like cLogP and pKa values within a desired range.
- Synthesized about 62 new analogs by Jubilant Chemsys and tested against Mtb (H37Rv strain) in last one year.
- Developed a limited understanding of pharmacophoric information based on MIC values of the new analogs
- Improved potency (MIC) wrt CDRI-830–the best compounds had MIC <1 µM
- Obtained pure enantiomers of CDRI-830 and tested for their antibacterial activities and one of them was found to be 4x more potent than the other one.
- Tested compounds for cytotoxicity against A549 and HepG2 cell lines- found narrow therapeutic window – scaffold is prone to show cytotoxicity

OSDD-29



OSDD-29 was identified as a new scaffold with MIC value of 12.5 µM against *M. tb.* H37Rv. Around 95 analogs of OSDD-29 were made at Jubilant Chemsys to develop SAR and identify the pharmacophore, toxicophore, etc. The inferences areas following:

1. Reasonable SAR – the scaffold has consistently shown good MIC values, but limited, SAR. The MIC data needs to be doubly checked to insure the values are real so that the scaffold can be progressed towards Lead Optimization.
2. Reasonably potent -MIC values are between 6.25-50 µM with some exception (targeted MIC to be <1µM)
3. Weak to moderate cytotoxicity - almost all compounds show some cytotoxicity with IC50s in the range of 170-390 µM
4. Good Safety margin wrt MIC – 10x-50x – acceptable for a lead at this stage.
5. Unknown Pharmacophore – pharmcophore emerging but not conclusive
6. Acceptable Lipophilicityrange - cLogP values 2.8-4.5

7. Too few H-Bond donors (HBDs) and H-bond acceptors (HBAs) – 1 and 2 respectively. Establishment of pharmacophore/toxicophore would allow increasing HBDs and HBAs in order to optimize potency, safety and properties to progress the scaffold towards LO phase. Poor PSA values – almost all compounds have PSA <30 (Ideal to have PSA between 50-80)

These compounds need to be tested for MIC and toxto validate the data.

OSDD-GSK Tress Cantos collaboration

Three scaffolds were decided to take forward under this collaborationand have been resynthesized at Jubilant Chemsys. Based on the screening results, OSDD-152 was prioritized while other two were deprioritised. About 8 analogs of the OSDD-152 scaffold have been synthesized and screened for anti-TB activity. The MIC shown are of the literature value.

Newly identified scaffolds

Through a stepwise screening of OSDD library of compounds against *M. smegmatis* at IICT followed by testing the hits against H37Rv resulted in a series of hits whose MIC values ranged from 5-100 uM. From this active list around 12 scaffolds have been prioritized for medchem activities. Thus far two of the hits, OSDD-170 and OSDD-173 along with a few of their analogs (total 27) were synthesized and tested against H37RV. Unfortunately they were found to be inactive.The remaining 10 prioritized hits are currently being synthesized for MIC confirmation.

g) Clinical Trials

CSIR- OSDD in collaboration with National Institute of TB & Respiratory Diseases (NIRTD), New Delhi is undertaking the Phase II clinical trials of a new combination therapy involving PA-824, Moxifloxacin & Pyrazinamide for MDR-TB patients. The open label clinical trials , whose final India specific protocol design was launched on World TB Day 2014 aims to evaluate the anti bacterial activity, safety, tolerability & pharmacokinetics of the combination. The primary objectives of the study are to o evaluate the anti-mycobacterial activity of a combination of PA-824, M and Z for the first 8 weeks in subjects with newly diagnosed pulmonary MDR-TB and evaluate the anti-mycobacterial activity of PA-824, when added to the Category IV regimen of RNTCP for the first 8 weeks, in subjects with newly diagnosed pulmonary MDR-TB. About 180 MDR male patients are to be recruited for the study, the screening for which is expected to begin in November 2014.

The study involves a 3- arm trial on MDR patients. The first arm constitutes Pa-M-Z while the second arm would consist of Pa plus DOTS plus regimen and third arm with DOTS plus regimen as control.

PaMZ has been taken up for clinical trials by CSIR-OSDD as it offers a promise of simpler, shorter and more effective regimen with fewer drugs. PaMz is active against both replicating and hypoxic, non-replicating Mtb and seen to have a sterilizing activity in human pulmonary TB.

Some major institutes other than CSIR- laboratories who are participating actively / contributing in the form of scientific inputs are:

National Institute of TB & Respiratory Diseases (NITRD), New Delhi
Tuberculosis Research Centre (TRC), Chennai
Indian Council of Medical Research (ICMR), New Delhi
All India Institute of Medical Sciences (AIIMS), New Delhi
National Institute of Immunology (NII), New Delhi

h) Status of Projects Under TATA Fellowship

Number of students has been selected under the TATA fellowship to work in the area of Drug Discovery. The selected fellows are associated with PIs who are running different projects under OSDD which have been scientifically reviewed and approved by its Scientific Review Committee.

Alternatively, the fellows may associate with projects which are at Proof of Concept stage. These short term projects, which are in line with the broad objectives of OSDD, may precede their submission to OSDD as full scale projects for support.

Broadly, the areas on which the fellows worked can be categorized as shown below;

The focus of majority of the projects was screening of compounds/ small molecules for anti-TB properties. These compounds were novel molecules, from medicinal plant extracts or were repurposed drugs. Similar efforts were undertaken for screening compounds for anti-malarial properties. In silico modelling of drug compounds was another area which the projects focused on.

In the process many students were trained in various aspects of drug discovery and development.

Summary of the Fellowship Programme

(A) TCOF
(B) TCOWF
(C) TCOS

Application Statistics (December 2013-till date)

(A) **TCOF**

Number of Applications received: 19
Number of Projects granted: 12
Number of fellows joined in the various projects: 35
Number of applications under review: 4

(B) **TCOWF**

Number of Applications received: 19

Number of Fellowships granted: 11
Number of fellows joined in the various projects: 11
Number of fellowships completed: 1
Number of applications under review: 4

(C) **TCOS**

Number of Applications received: 47
Number of Fellowships granted:27
Number of fellowships completed: 27
Number of applications under review: 20

Status of TCOF, TCOWF and TCOS Fellowships (December 2013-till date)

TCOF

PROJECT ID	NO. OF FELLOWS	NAME OF THE FELLOW	NAME OF THE P.I.	NAME OF THE PROJECT	PROJECT UPLOADED DATE	PROJECT STARTING DATE	PROJECT ENDING DATE	PROJECT STATUS
TCOF 1	2	Mr. Nufail Mr. Ajay K Mathias	Prof. Jayaraj P. B.	Development of Parallelization Algorithm for Random Forest to run on CUDA atmosphere for ligand based drug discovery.	10-12-2013	01-01-2014	Will be decided after review	Project Running Successfully
TCOF 2	2	Ms. S Priyanka Mr. Banka Janardhanareddy	Dr. Anthony Addlagatta	Discovery and Development of Mtb Specific Methionine Aminopeptidase Inhibitors.	10-12-2013	05-12-2013	Will be decided after review	Project Running Successfully
TCOF 3	7	Mr. Sajeev R Ms. Swati Gandhi Ms. Rakhila Mr. YatindraYadav Ms. Aisha Safeeda Mr. Lijo John Mr. Chadnan Kumar DN	Dr. U.C. A. Jaleel	Repositioning Different Chemical Classes for Anti Tb Virtual Screening.	10-12-2013	05-12-2013	Will be decided after review	Project Running Successfully

TCOF 4	7	Ms. M. Prashanthi RamasreeDulapalli Mr.A. SrinathRaju Ms.SonaAjith MsJayanthiJayakumar Ms.Chithra Krishnakumar TanusreeModak	Dr. G. NarahariSastry	Chemo-Informatics, Structure Based and Molecular Dynamics Approaches for Lead Identification and Optimization for Infectious Diseases	10-12-2013	20-12-2013	Will be decided after review	Project Running Successfully
TCOF 5	6	SatyaAnilaNallam Ms. C. Rekha Ms. Asita Singh Ms. SudhaSravanti Mr.KKiranBabu Ms. PapulammaPamba	Dr. Ramesh Ummanni	Screening and sample management of small molecule libraries for identifying novel anti mycobacterial agents.	10-12-2013	23-12-2013	Will be decided after review	Project Running Successfully
TCOF 6	1	Tony Roy	Dr. Akkattu T. Biju	Transition-Metal-Free Synthesis of Five and Six-Membered Heterocycles	11-12-2013	13-01-2014	Will be decided after review	Project Running Successfully
TCOF 8	1	NIL	Dr. K. V. Radhakrishnan	Transition metal catalyzed transformations of heterobicyclic olefins	11-12-2013	13-01-2014	Will be decided after review	Project unable to start due to technical reasons

TCOF 9	3	Pankaj Mishra Mangya Ram & Deepak Sharma (Under Process)	Dr. Gautam Panda	CDRI-830 Analogs Synthesis and Bioevaluation	11-12-2013	13-01-2014	Will be decided after review	Project Running Successfully
TCOF 10	2		Dr. Balaraman Deivasigamani	ISOLATION CHARACTERIZATION OF PROTEOMIC COMPUND FROM MARINE FINFISH AND SHELLFISH IN SOUTH EAST COST OF TAMIL NADU	11-12-2013	NA	NA	Project Rejected
TCOF 11	1		Dr. Satyendra Kumar Pandey	Structure-Based Design and Synthesis of 2-alkyl-substituted Tetrahydroquinolines as Antimalarial Agents	11-12-2013	NA	NA	Project Rejected
TCOF 12	3	Iti Gupta Mohd Ahmad HaeshaRohira	Dr. Anshu Bhardwaj, Dr.Swati Subodh	Analyzing the transcriptional and structural implications of select nucleotide polymorphism in the drug metabolizing and transporter genes: An in-silico study	11-12-2013	13-01-2014	Will be decided after review	Project Running Successfully
TCOF 13	1	Surendra Kumar	Dr. UrmiBajpai& Dr. Andrew M Lynn	Virtual screening & in-vitro assays for inhibitors of Mur Enzymes	18-12-2013	13-01-2014	Will be decided after review	Project Running Successfully
TCOF 14	3		Dr. Ratnesh		18-12-2013	NA	NA	Project Rejected

TCOF 15	2	Mayakrishnan S Kandhasamy S	Dr.P.T.Perumal	To Design, Synthesis, and Structure—Activity Correlations of Novel 1, 4, and 1, 5-triazoles from Lawsone and Embeline as Potent Inhibitors of Mycobacterium tuberculosis and Activity Against Select Cancer Cell Lines.	18-12-2013	24-01-2014	Will be decided after review	Project Running Successfully
TCOF 16	1		Dr. GeethaVani Rayasam	Development of small molecule drugs that target type VII secretion in Mycobacteria	02-01-2014	NA	NA	Project Under Process
TCOF 17	2		Vijay Nair	Diversity Oriented Synthesis of Biologically and Pharmaceutically I mportant Heterocyclic Molecules	28-02-2014	NA	NA	Project Under Review
TCOF 18	2		Dr. Santosh B. Mhaske	Quinolino-carbonline Derivatives for SAR Studies in Search of Novel Antitubercular Drug Candidates	04-03-2014	NA	NA	Project Under Review
TCOF 19	1		Dr. Ritta Mathew	Screening compounds against M.smegmatis biofilms	13-05-2014	NA	NA	Project Under Review

TCOWF

PROJECT ID	NAME OF THE FELLOW	NAME OF THE P.I.	NAME OF THE PROJECT	PROJECT UPLOADED DATE	PROJECT APPROVED DATE	PROJECT STARTING DATE	PROJECT ENDING DATE	PROJECT STATUS
TCOWF 1	Kanchana Srivastava	Dr.Suryakanth & Dr. Kishore K Srivastava	Phylogenetic studies of Mycobacterium tuberculosis isolates on the basis of Insertion sequences, Direct repeats and Variable Number of Tandem Repeats in Pulmonary and extra-pulmonary Patients.	12-11-2013	01-01-2014	14-03-2014	Will be decided after review	Project Running Successfully
TCOWF 2	Tanusree Chaudhuri	Dr. Abdul Jaleel U.C	Creation of integrated cross-platform cheminformatics software with Avogadro and Autodock.	12-11-2013	01-01-2014	01-02-2014	Will be decided after review	Project Running Successfully
TCOWF 3	Roshni Bhatt	NO PI	The Mycobacterium tuberculosis Drugome and Its Human System Biology Implications.	12-11-2013	NA	NA	NA	Project Rejected
TCOWF 4	Dhanalakshmi M	NO PI	Computational Study-Structral Complexities In Certain Biologically Important Sugar Derivatives.	01-02-2014	NA	NA	NA	Project Rejected

TCOWF 5	PrijaPonnan	NO PI	Computer Aided drug design using QSAR, Pharmacophore modeling, Fragment based drug design, docking and molecular simulations to develop drug molecules against Tuberculosis, Malaria and other tropical neglected disease.	01-02-2014	NA	NA	NA	Project Rejected
TCOWF 6	NibeditaRath	Dr. BheemaraoUgarkar	Identification of novel inhibitors for M. tuberculosis ndh2 (NDH-II).	29-01-2014	05-04-2014	11-04-2014	Will be decided after review	Project Running Successfully
TCOWF 7	ChitraThaneerkulam	Ms. Dakshayani S. Pradhan	Communication Strategies For Osdd In Reaching Out To The Public.	29-01-2014	05-04-2014	11-04-2014	Will be decided after review	Project Running Successfully
TCOWF 8	Sona Charles	NO PI	Systems Biology Of Host- Pathogen Interactomics In M. Tuberculosis: A Network Based Approach To Classify Hub And Non-Hubs In Bacterial Infection.	25-02-2014	NA	NA	NA	Project Rejected

TCOWF 9	Sonali Gupta	NO PI	Determination of protein three-dimensional structure and determination of possible binding ligands through in silico protein-ligand docking.	26-02-2014	NA	NA	NA	Project Sent to Expert Committee for Review
TCOWF 10	Ekta Singh	Dr. Andrew Lynn	Collection of biologically relevant mutation associated with TB disease susceptibili ty and development of GWAS pipelines.	10-03-2014	16-05-2014	06-03-2014	Will be decided after review	Project Running Successfully
TCOWF 11	Roopa Singh	Dr. Andrew Lynn	Development of a Virtual screening platform using open source docking software and application to identify potential drug like inhibitors against OSDD shortlisted targets.	03-10-2014	16-05-2014	06-03-2014	Will be decided after review	Project Running Successfully
TCOWF 12	Sunita Gupta	Dr. Andrew Lynn	Post Processing of Docked complexes using BEAR Algorithm.	03-08-2014	16-05-2014	08-03-2014	Will be decided after review	Project Running Successfully
TCOWF 13	Akshata Gad	Dr. Abdul Jaleel U.C	Support-System Fellow for Medicinal Chemistry and Cheminformatics Activities of OSDD.	11-04-2014	16-05-2014	01-08-2014	Will be decided after review	Project Running Successfully

TCOWF 14	Ankita Ray	Dr. UrmiBajpai	Investigating the diversity of Mycobacteriophages in India and exploring their potential as source for anti-Mycobacterial active biomolecules. A pilot study.	11-04-2014	16-05-2014	01-05-2014	Will be decided after review	Project Running Successfully
TCOWF 15	DivneetKaur	Dr. Samir K. Brahmachari	Designing Non-Toxic Ligands for Targets Identified based on Systems-Level Analysis of Metabolism in Mycobacterium tuberculosis.	22-04-2014	16-05-2014	26-05-2014	Will be decided after review	Project Running Successfully
TCOWF 16	Srota Dawn	Dr. Srinivasan	Synthesis and evaluation of Antitubercular activity of Heterohexose analogues & derivatives.	12-05-2014	NA	NA	NA	Project Under Review
TCOWF 17	Jisha M	Dr. Ritta Mathew	Screening compounds against M.smegmatis biofilms.	26-08-2014	02-09-2014	NA	NA	Project Approved
TCOWF 18	Kochurani K J	Not yet allotted	ABC TRANSPORTERS OF M. tuberculosis AS DRUG TARGETS IN DRUG RESISTANT TUBERCULOSIS – AN INSILICO APPROACH.	24-06-2014	NA	NA	NA	Project Under Review
TCOWF 19	ParakhKartik Sharma	Mr. Pushpadeep Mishra (IIT Bombay)	Development of virtual assay database.	26-08-2014	NA	NA	NA	Project Under Review

TCOS

TCOS ID	Name	Project Name	Starting Date	Ending Date	Status
TCOS 1	Andrew Titus Manuel	Strategies For Imparting Communication Net For Community Development And Scientific Output In OSDD	20-01-2014	Will be decided after review	Project Completed
TCOS 2	Akshata Gad	Virtual Screening of the Inconclusive Data of PubChem Bioassays	31-01-2014	Will be decided after review	Project Completed
TCOS 3	SyedaMeraj	Database of chemical compounds and their properties tested possitive for MTB culture	31-01-2014	Will be decided after review	Project Completed
TCOS 4	Nilavazhagan .A	Structural Examination of OSDD prioritized TB targets	31-01-2014	Will be decided after review	Project Completed
TCOS 5	AswathySivanandan	Identification of Dihydropicolinate Synthase and Reductase Inhibitors: A Modelling and informatics Approach	20-01-2014	Will be decided after review	Project Completed
TCOS 6	AvatapalliSaiSupriya	Identification of Protein kinase B and 2, 3-dihydroxybenzoate-AMP ligase inhibitors: A Modeling and Informatics Approach	20-01-2014	Will be decided after review	Project Completed
TCOS 7	DibiMol Thomas	Synthesis and biological evaluation of substituted benzoylfumarate derivatives against Mycobacterium tuberculosis	21-01-2014	Will be decided after review	Project Completed
TCOS 8	Neethu K. M	Palladium Catalyzed Synthetic Transformations of Diazabicyclic olefins using Catechols	21-01-2014	Will be decided after review	Project Completed
TCOS 9	Sidheekha M. P.	Synthesis of Spiro-dioxepine fused 2-Oxindole: An important structural core in Medicinal compounds	21-01-2014	Will be decided after review	Project Completed
TCOS 10	Divya Chandran A	Optimization of Antimalarial Activity of 4-Aminoquinoline derivatives: QSAR, GUSAR, and CoMFA analyses	01-02-2014	Will be decided after review	Project Completed
TCOS 11	Rajeev M.R.	In silico methods to evaluate the Anti-malarial activity of some herbs used in traditional medicines	01-02-2014	Will be decided after review	Project Completed
TCOS 12	Arunabh Sharma	Integrated Web Server for screening molecules against TB targets	31-01-2014	Will be decided after review	Project Completed
TCOS 13	Manu Thomas	Development of OSDD BQ3 and OSDD BQU	NA	NA	Project Under Review
TCOS 14	HemaNaripatta	Synthesis potent antimycobacterial derivatives that are designed around the pyrrole core	NA	NA	Project Under Review

TCOS 15	KasaganiVaraprasad	Synthesis of unprotected beta-C-allayl- and beta-C-propargyl-D-arabinfofuranosides(1&2)(scheme 1) and long chain carba-analogues 3	NA	NA	Project Under Review
TCOS 16	JaliparthiSrilakshmi	Metal C-C bond formation via activation of SP2 C-H bonds of 1,2,4-oxadiazoles derivatives and its application to the Synthesis of Small-Molecule and testing against Tuberculosis	NA	NA	Project Under Review
TCOS 17	Jaya Uniyal	Probing the Intrinsic Resistome of Mycobacterium tuberculosisMapping of chemical space, modeling and simulation of metabolism and predictive models of influx as filters for drug-like molecules	01-03-2014	Will be decided after review	Project Completed
TCOS 18	Shilpi Singh	Structure based virtual screening and in-vitro assays to identify inhibitors against M.tbMurA and MurE enzymes	06-02-2014	Will be decided after review	Project Completed
TCOS 19	HemasriSinguluri	Design of Target Specific Filters for Designing Anti- Tb Inhibitors	11-02-2014	Will be decided after review	Project Completed
TCOS 20	JyotiRanjanSahoo	Natural product fragments and scaffolds for design of anti-TB inhibitors	11-02-2014	Will be decided after review	Project Completed
TCOS 21	Jayasankari .S	Development Of Anti-Malarial Compounds By Pharmacophore Fingerprint Based Virtual Screening With Special Emphasis On M18 AspartylAminopeptidase	NA	NA	Project Under Review
TCOS 22	Hari Prasad P.M	Synthesis Of focussed molecular libraries	05-02-2014	Will be decided after review	Project Completed
TCOS 23	ParameswariBehera	Fragment based design of potent anti TB inhibitors	11-02-2014	Will be decided after review	Project Completed
TCOS 24	KuhooBarao	Purification,Characterisation,Biotransformation and Screening of Lanceol and its metabolites for Anti-TB activity from sandalwood oil	05-02-2014	Will be decided after review	Project Completed
TCOS 25	Sanjay Sahu	Investigation of polymorphs and Co-crystals of Anti-TB drug :An attempt to improve their physicochemical properties	05-02-2014	Will be decided after review	Project Completed
TCOS 26	DishitaAshar	Development of virtual assay database	04-02-2014	Will be decided after review	Project Completed
TCOS 27	Nidhi Pant	Development of virtual assay database	04-02-2014	Will be decided after review	Project Completed
TCOS 28	Anudeep S	Development of Promiscuity Server for Drug Discovery	NA	NA	Project Under Review
TCOS 29	Vidya P.M	Development of Promiscuity Server for Drug Discovery	NA	NA	Project Under Review

TCOS 30	Harsha HR	Implementation of jmol to display 3d structure of chemical molecule	NA	NA	Project Under Review
TCOS 31	Harish Babu C	Integrated Cross Platform Gui For Cheminformatics	NA	NA	Project Under Review
TCOS 32	Sathyanarayana.B.S	Development of Promiscuity Server for Drug Discovery	NA	NA	Project Under Review
TCOS 33	ShruthiMol K	Development of Promiscuity Server for Drug Discovery	NA	NA	Project Under Review
TCOS 34	Ameera CM	Implementation of jmol to display 3D structure of chemical molecule	NA	NA	Project Under Review
TCOS 35	Akhi Joy	Integrated Cross Platform Gui For Cheminformatics	NA	NA	Project Under Review
TCOS 36	Ranjani.M	Comparative study on different Structure activity relationship (SAR) model development tools using Artificial Intelligence techniques	NA	NA	Project Under Review
TCOS 37	MithunmohanKadavilmadanamohanan	Clustering Large Protein-Protein Interaction Network With CsrSparse Format Using GPU	NA	NA	Project Under Review
TCOS 38	Sandeep Narayan P	Finding Hub Proteins And Their Interactions In A Protein-Protein Interaction Network Using GPU	NA	NA	Project Under Review
TCOS 39	KambhamVenkateswarlu	Investigation To Fabrication And In Vitro Bioequivalence Studies Of TenofovirDisoproxilFumarate Tablets	NA	NA	Project Under Review
TCOS 40	AnchuSobhan A.S	QSAR Modelling Of Active Molecules To Inhibit Nat 2 As A Drug Target Against Mycobacterium Tuberculosis	NA	NA	Project Under Review
TCOS 41	Neethu M. S	In Silico Studies On The Activities Of Ruthenium(Ii) Phosphine/Diimine/Picolinate Complexes (Scar) Against Mycobacterium Tuberculosis	NA	NA	Project Under Review
TCOS 42	Anusha P. M	Homeopathy In Multi Drug Resistance PulmonaryTuberculosis and to find out the most efficacious drugs with their reliable indication, potencies and frequency of administration	NA	NA	Project Under Review
TCOS 43	Sooryalekshmi S	Computational screening on the phytomole as lead molecule for the design of inhibitors against mycobacterium tuberculosis from Allium Sativum	NA	NA	Project Under Review
TCOS 44	Radhika.R	Anti-Tuberculosis Evaluation of Piperine from Piper Longum	NA	NA	Project Under Review

TCOS 45	Vishnu Surendran	Computational screening on the phytomole as lead molecule for the design of ? – lactamase inhibitors against mycobacterium tuberculosis from Aloaceae	NA	NA	Project Under Review
TCOS 46	Athira Ramesh	Check The Druggability Of The Molecules In 5 Medicinal Plants	NA	NA	Project Under Review
TCOS 47	Subi.B.S	InsilicoModelling Of Anti- Tuberculosis Active Molecules	NA	NA	Project Under Review

8. OSDD- Other Activities

OSDD's Special Science Reporter Issue

Reaching out to the large cross section of students at higher secondary and graduate levels, CSIR-OSDD in collaboration with CSIR-NISCAIR published a special issue of Science Reporter in April 2014. The issue called '*CSIR's Open Source Drug Discovery Programme: Changing the rules of drug discovery'* aims to simplify the process of drug discovery to young students through popular science articles. The issue contains a compilation of articles from various PIs and students of OSDD and describes the activities of OSDD in an easy to comprehend manner.

OSDD –VP Essay Competition

Besides core scientific activities, CSIR- OSDD has been actively conducting various outreach programs aimed at creating awareness regarding TB and Malaria and need of new drugs for the same. Under this effort CSIR-OSDD in collaboration with Vigyan Prasar successfully conducted a YouTube based short video competition on "The Need of New Drugs for Tuberculosis" for the second time in December 2013. The contest saw wide scale participation from individuals and institutes across the nation.

In the same series, CSIR- OSDD, in collaboration with Vigyan Prasar is currently conducting a Hindi Essay competition on **"**मलेरिया-एक चुन्नौती एवं निवारण के उपाय**"** for school students. The contest aims to spread awareness regarding Malaria among students. . The contest which is open to students from class 8th to 10th requires the participants to compose a Hindi essay on Malaria, related challenges and preventive measures shedding light on issues prevalent in their localities.

Training and Skill Development

As a part of the outreach program, OSDD is actively engaged in conducting drug discovery workshops and virtual classes in Various Universities and Colleges throughout India. As a part of this CSIR-OSDD Research Unit, IISc, Bangalore has conducted following seminars and workshops.

(a) Seminars on Drug Discovery

- SASTRA University, Tanjore
- SN College,Varkala
- SN College,Chengannur
- SS College, Kannur University
- Academy of Chemistry Teachers, Kerala

(b) In House Workshops

- Medicinal Chemistry students of Kerala University, at CSIR-OSDD Research Unit, IISc, Bangalore.
- Drug Discovery seminar for Sir Syed College of Taliparamba, at CSIR-OSDD Research Unit, IISc, Bangalore.
- Students of NIT Calicut.

CSIR-OSDD has also undertaken the task of training students, teachers, researchers, scientists, and the community at large. Training was imparted to 22 students from various universities and colleges who completed their academic projects at OSDD Unit, Bangalore and 10 open lab interns in the disciplines of Cheminformatics, Data Mining, Drug Discovery and Web based applications related to Medicinal Chemistry as in house projects at CSIR-OSDD Research Unit, Bangalore. The results are published in open blogs for public view.

Community Outreach Programs

Besides formally collaborating with numerous international institutes, CSIR-OSDD encourages unconventional techniques of learning and knowledge sharing. Leveraging on the strengths of social media, OSDD is connected globally to experts in the area of drug discovery like CDD and fragment based drug discovery group. CSIR-OSDD Research Unit at Bangalore is also tapping on the creative potentials of students to use extra-curricular activities like music to promote Open Science activities.

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