Drug discovery is a multidisciplinary and multi-step process that begins with identifying good chemical starting points called Hits or Leads, which are discovered mostly through screening a large collection of compounds of diverse chemical structures. There are different lead generation approaches in drug discovery i.e. substrate structure based, random screening (whole cell and target based) and literature information based approaches.

Substrate structure based approach uses the knowledge of substrate structure to design the substrate analogues to compete with substrate of protein target. The whole cell screening approach is based on identifying inhibitors from particular cell phenotype such as inhibition of cell growth upon treatment with the compounds.

Predictive science uses different criteria to select the target of interest. Medicinal chemistry knowledge is used to design inhibitors for such predicted targets. Lead generation approaches can also be devised from literature information.

In OSDD, all the lead generation approaches described above are being used.

**Antibacterial Drug Discovery**

Drug discovery and development of new antibacterial agents have displayed dismal success rates as evidenced by USFDA approvals of only a handful of new antibiotics (e.g., Linezolid, Bedaquiline, etc.) in the last two decades (*Nature Reviews Drug Discovery*, 2007, 6, 29). While the chief cause of this failure can be attributed to the lack of new druggable targets, the lack of chemical diversity of the compound libraries used for screening against whole cells or biochemical targets has made the situation worse.

The compound libraries of large pharma companies are biased toward finding good hits for metabolic diseases and other non communicable diseases including cancer, diabetes, obesity, etc., where success rate and returns on investment are high. When such libraries are screened against whole cell pathogens or their biochemical targets in antibacterial drug discovery, the outcome is predictably poor.

This scenario leads one to ask: Is it possible to design a 'library of compounds for infectious diseases including tuberculosis' that will increase chances of success in finding robust antibacterial starting points?

The answer to this question is not very definitive because existing antibacterial agents encompass a variety of structural classes. For example, the historical antibacterials are natural products that fall mainly into three or four structural classes – aminoglycosides (streptomycin and the like), beta-lactams (penicillin class), macrolides (Rifampicin, vancomycin, erythromycin, etc.) and chloramphenicol analogs, whereas, man-made antibiotics form the classes such as sulphonamides, fluoroquinolones, oxazolidines (Linezolid), etc.

Analogos of all these compounds have already been tested, resulting in a small number of new antibiotics that were successfully brought to clinic. Furthermore, second-generation analogs of the existing antibiotics demonstrate poor or no efficacy against drug resistant pathogens. Hence it is important to venture outside these scaffolds to find molecules that work via novel drug targets, consequently increasing the chances of discovering antibiotics to treat drug resistant pathogens. This is particularly true in case of tuberculosis.

Though few recent publications have reported compounds against Mtb (*ChemMedChem*, 2013, 8, 313; *ChemMedChem*, 2011, 6, 2252), new chemical libraries having diverse structures are essential for identification of novel compounds to target TB.

To achieve this end, OSDD has undertaken a chemistry initiative to create its own chemically diverse compound library to screen against Mtb and Malarial parasite.
Open Source Drug Discovery (OSDD) foresees building of a chemically diverse compound library which could greatly aid the project's drug discovery process.

Compound Library

OSDD started an initiative called the ‘OSDD Chemistry Outreach’ in 2011, which aimed at creating a library of unique structures by harnessing chemistry expertise available in India. India has a rich tradition in synthetic chemistry with which it has made a phenomenal impact in reducing the cost of life-saving drugs worldwide by creating a very strong presence in the generic drug industry.

Besides, a steady rate of high quality patents and publications coming out of India is also a testimony to the exceptionally talented synthetic chemists working in various institutes across India. It is this talent OSDD is attempting to tap in creating a drug discovery environment to make an even bigger impact in bringing out affordable new medicines, particularly to neglected diseases that have a great impact in India.

OSDD Chemistry Outreach Centers are located in CSIR laboratories as they are well equipped to carry out the necessary chemistry activities. The programme is led by the CSIR-Central Drug Research Institute at Lucknow.

The aim of the programme is to recruit talented undergraduate and graduate students, academic faculties in various universities and scientists in institutes like CSIR laboratories, IITs, NIPERS, IISERs, etc., to design and synthesize compounds for screening activities. This initiative provides opportunities to students to train under highly accomplished scientists to gain laboratory experience and learn to use modern equipment and techniques available.

A small team of dedicated OSDD scientists with drug discovery experience is in place to help participating students acquire training in various aspects of drug discovery sciences. Students are recruited as short-term interns based on their academic merit, knowledge of chemistry discipline, etc. After successful completion of the training the participating students receive a certificate of achievement.

The programme is designed to make small molecules in 2-3 simple steps in pure form and submit them for screening activity. Often common intermediates are employed to synthesize a library of compounds with different properties. This approach, commonly known as diversity-oriented chemistry, has been successfully applied in generating not only screening
libraries but also compounds for SAR (Structure Activity Relationship) studies for advanced drug discovery projects.

The chemistry project formulation and screening involves the following steps:

1. Become a member of the OSDD community. Guidelines are provided on the OSDD portal (http://www.osdd.net/). The guidelines for proposal writing include a historical background, sound rationale behind the proposal, a work plan, defined deliverables, timelines, personnel, funding requirements, etc.

2. Submit a research proposal. Proposals are submitted online to the OSDD portal.

3. Evaluation of the proposal. Proposals are open to registered OSDD members to evaluate and provide comments and suggestions.

4. Funding decision. An OSDD team of scientists too will evaluate the proposal before making the funding decision. The decision is communicated to the principal investigator/s (PIs) of the project in a timely fashion.

5. Monitoring the project progress. Work is monitored periodically through meetings, and necessary changes are suggested wherever appropriate.

6. Submission of compounds to compound repository (Molbank). Standard Operating Procedure (SOP) for compound submission is located on the OSDD portal. All the relevant analytical data supporting purity and authenticity of structure are made available on the OSDD portal before submitting the compound. The compounds are stored in CDRI Mol Bank and are tested against TB and malaria.

All the activities of project proposals, virtual compounds from the project, compounds synthesized, expert comments, project sanction, synthesis, screening and toxicity test results are made available on the OSDD portal. The link http://crdd.osdd.net/osddchem/ describes the OSDD Chemistry Outreach programme.

**Current Status**

Currently more than 80 scientists along with their research teams from various academic institutes and CSIR laboratories are involved in building the compound library. The largest team of 25 PIs is working from IICT. Different individual projects from a CSIR laboratory constitute an umbrella project. The individual proposals are subjected to due processes of evaluation, funding and monitoring of work plans periodically.

The proposed compounds are synthesized and submitted to the Molecular Bank at IICT. Pertinent analytical information on each of the compounds is provided on the OSDD
OSDD Chemistry Outreach Programme provides opportunities to students to train under highly accomplished scientists to gain laboratory experience and learn to use the most modern equipment and techniques available. OSDD Chemistry Outreach Centers are located in CSIR laboratories as they are well equipped to carry out the necessary chemistry activities.

OSDD is currently collaborating with PIs from CDRI Lucknow on a molecule (CDRI-830) they have discovered through screening of their library of compounds followed by optimization of potency against Mtb cells. CDRI-830 has also demonstrated good intracellular activity and efficacy in the animal model of tuberculosis. With a view to improve potency and physicochemical properties, OSDD has accessed Jubilant’s synthetic chemistry capabilities to make new analogs, and Premas for profiling compounds for their antibacterial properties.

More than 130 new analogs are made to further the goals of the project. A team from IICT is spearheading the testing of these compounds in cytotoxicity assays to ensure that toxicity information is fed into the project work in continuous fashion for designing new analogues.

OSDD’s goal is to harness the best talent available in India to discover and deliver affordable medicines to treat neglected diseases that affect the most in India, and we anticipate full participation from wider scientific communities all over the world.

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Portals called OSDDChemDesign. Each of the compounds is assigned a unique compound identification number and an accession code. The IICT-Mol bank experts help in storing, bar coding as well as dispensing the compounds for biological testing activities.

The screening strategy for tuberculosis involves testing compound libraries first against Mycobacterium smegmatis, which is a non-infective, surrogate organism of the highly infective and disease causing Mycobacterium tuberculosis (MtB). The compounds that show more than 30% inhibition of M. smegmatis at 30 μM are further tested against MtB. Compounds that show potent MIC values (MIC <16 μg/mL) are prioritized for Hit Evaluation (HE) process.

Till now under the whole cell screening, 8500 compounds are screened against M. smegmatis where 350 compounds showed more than 30% inhibition at 30 μM. The 530 positives were further tested against MtB and 117 compounds that showed inhibition were identified. 11 scaffolds from the 117 were prioritized to take them further. HE process involves making a small number of structurally close analogs of the hit and testing them directly against MtB. Robust hits are the ones that show a graded MIC against MtB reflecting an emerging SAR, thus raising the confidence that the molecule has a real antibacterial effect and tolerates changes to the structure which are necessary for improving potency and properties as the molecule progresses on the drug discovery path.

In addition, the promising scaffolds reported in literature are analyzed and proposed to PIs so that they can be taken forward. The predicted biological targets are also used as the starting point to develop programmes to generate inhibitors.

Several projects are pursued in structure-based drug discovery stream. The examples include inhibitors for NAD dependent DNA ligase of MtB, DAP A and DAP B inhibitors, inhibitors for fatty acyl-AMP ligases (FAALs) and fatty acyl-CoA ligases (FACLs) of MtB, and inhibitors for MtB N-acetylglucosamine-1-phosphate uridylyltransferase (GlmU). In all the above projects structural biology based information is used to design the molecules. Such molecules are then synthesized and tested for enzyme inhibition as well their ability to inhibit MtB cells.

OSDD’s Medicinal Chemistry team analyses all the biological data, interprets the results and devises ways to take the hits forward in collaboration with PIs. A detailed project involves a continuous process of making compounds and testing. Thus a Design Make Test and Analyze (DMTA) cycle is created to make a steady progress of drug discovery projects.

Partnering with CRO to Bridge Gap in Drug Discovery

The important objective of OSDD is to facilitate discovery of new drugs to treat neglected diseases in a collaborative fashion. In order to augment PIs’ efforts, resources of Contract Resource Organizations (CROs) are recruited so that a dedicated team is deployed to make and test molecules in fast DMTA cycle. Currently OSDD is partnering with Jubilant Chemsys for synthetic chemistry, Anthem Biosciences for biochemical work and Premas Biotech for microbiological work.

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