Open Source Drug Discovery: Model for Novel Drugs against Neglected Diseases

Geetha Vani Rayasam, OSDD Consortium and Tanjore S. Balganesh

Translating novel ideas into clinical settings through robust drug discovery projects is the challenge that the Open Source Drug Discovery project is focusing on. OSDD has the potential to emerge as a major alternative for the development of drugs for neglected diseases and bring in much needed new drugs and regimens for afflicted Indian patients.

Even today many infectious diseases like Tuberculosis (TB) are a major problem in India. India has more new TB cases annually than any other country.

In 2011, out of the estimated global annual incidence of 9 million TB cases, 2.3 million were estimated to have occurred in India. Annually, about 270,000 patients die of TB in India. Even though drugs for TB are being administered under direct observed treatment short course (DOTS) therapy as per Revised National TB Control Programs (RNTCP) guidelines, high levels of drugs resistance are being encountered.

Treatment of TB with the first line treatment consists of a combination of four drugs (Isoniazid, Rifampicin, Ethambutol and Pyrazinamide) lasting about six months. The drugs used are associated with several side effects. Given the prolonged duration of therapy and the associated side effects, patient compliance is poor. This results in inadequate drug
SysBorg 2.0 is OSDD's cyber infrastructure for collaborative research. SysBorg has over 7,900 participants from 130 countries across the world. Join SysBorg 2.0 in order to know more about the ongoing activities of OSDD, view results of experiments, and participate in research projects.

OSDD Chem is the web interface for large-scale synthesis of diverse chemical compounds to screen them against TB and Malaria. Log into OSDD Chem using your SysBorg OpenID to know more about submitting molecules and project proposals.

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Message from Chief Mentor, OSDD

"I believe that affordable healthcare is a right for all. But, pragmatically speaking, when it comes to health, we need to have a balanced view between health as a right and health as a business." Read More

exposure, which in turn triggers drug resistance, wherein they do not respond to the drugs being given during treatment.

For multi drug resistant (MDR) TB patients, who are resistant to first-line drugs INH and Rif, the treatment with second-line drugs is for at least 24 months with a combination of 5 drugs under the DOTS PLUS regimen (a fluoroquinolone, ethionamide, pyrazinamide, cycloserine or PAS and an injectable – Capreomycin/ Kanamycin/Amikacin) that have many side effects. There are very few treatment options available for XDR TB patients who are resistant to both first- and second-line drugs.

With the strong foundation laid so far across various disciplines and having built a drug discovery portfolio and initiated clinical trials for TB, OSDD has the potential to emerge as a major alternative for the development of drugs for neglected diseases at affordable treatment.

No new drugs have been discovered for TB over several decades, as TB is perceived as a disease of the poor and there is no return of investment for pharmaceutical companies to invest in it. This calls for alternative innovative strategies for development of new drugs for neglected diseases like TB outside of the pharmaceutical industry.

With this objective in view, the Council for Scientific and Industrial Research (CSIR) initiated the Open Source Drug Discovery (OSDD) programme on 15 September 2008. Under this initiative, drug discovery would be performed in a collaborative manner involving several academic partners and contract research organizations (CROs) where data would
be shared in an open manner not restricted by intellectual property (IP) and patents. Clinical trials would be conducted and drugs that would be developed under OSDD would be made available similar to generic drugs, so that the drugs would be affordable to the patients.

OSDD is now an internationally recognized drug discovery programme for neglected diseases with about 7950 registered participants from over 130 countries. More than 100 Principal Investigators are working on various aspects of TB drug discovery (details on website, www.osdd.net).

**OSDD Operational Model**

The success in bringing new molecules for the treatment of neglected diseases would require paradigm shifts in the therapy. This would require nurturing and progressing novel and innovative ideas, science that needs to be translated into drug discovery and clinical experimentation. OSDD attempts to deliver on this paradigm.

The major strengths of the OSDD model are:

- It’s ability to work through ‘crowd sourcing’ of ideas for drug discovery and building web-based platforms that enable active exchange of information and comments which are accessible to the entire OSDD community
- Its core competence in converting academic ideas and information into robust drug discovery programmes
- Building a variety of facilitating platforms that help all OSDD partners to access the drug discovery enabling technologies
- Underpinning all this is the role of ‘informatics’ – cheminformatics and predictive sciences, which will form the basis of the ability to increase chances of success as well as reduce the time to deliver.

Through this approach, OSDD builds on the academic strength of its partners from various institutions across India and incorporates a robust drug discovery progression path to evaluate and progress promising ideas and molecules.

Now, why is this approach most suited for finding new therapies for Neglected Diseases? Treatments for Neglected Diseases like Tuberculosis, Malaria and Leishmaniasis have undergone limited advancement over many decades in spite of the tremendous advances that have been made in the understanding of the biology of the disease as well as in the approaches to find new therapies. The limited advances we have seen are still incremental and fail to address major lacunae like the ‘prolonged duration of therapy’ or the diagnosis or prognosis of the diseases. This is because of the ‘neglected’ nature of the afflicted population as well as the complexity of the disease, which requires new science to address the arsenal of the pathogen.

Translating novel ideas into clinical settings through robust drug discovery projects is the challenge and we at OSDD focus on this deliverable. We believe the fundamental source of innovation would be the ‘crowd sourcing’ ability.

**Building and Delivering through OSDD**

While the programme is envisaged in three phases, the first phase involved focusing on one of the neglected diseases, Tuberculosis, and creating platforms and involving researchers to participate in this venture through the new model. Additionally, establishing infrastructure to progress value projects as well as create pathways to screen for starting points were key activities during this period.

A major emphasis has also been to build on the chemistry strength of the community by building chemically diverse libraries and incorporating informatics-based analytical processes on the data. These activities were largely completed during the first phase of the programme.

The second phase of the programme involves expanding the activities both in the number of projects and also in the number of diseases, both Malaria and Leishmaniasis, and to support novel diagnostic opportunities for these diseases. Additionally, activities in the translational area are sought to be focused during this period in order to be able to bring the desperately needed drugs to patients.

As the number of platforms increase to meet the demands generated by the discovery process, a number of OSDD hubs at different CSIR laboratories are also envisaged.

**OSDD’s ability to bring a paradigm shift in the treatment of neglected diseases will depend upon finally translating novel drugs and regimens in the clinical setting.**
A strategy to introduce novel drug combination regimen for the treatment of TB patients is the unmet medical need; this approach would be a paradigm shift over the conventional path, which involves introducing one new drug at a time to an existing combination.

The third phase is envisaged to focus mostly on the later stages of drug development involving multiple clinical trials in Phase 2 and Phase 3. This will involve researchers at multiple clinical sites being coordinated through the OSDD umbrella. This will also be the period to probe novel ideas in other disease areas where the same model in most needed.

Activities under the OSDD model primarily revolve around Predictive Sciences, Discovery Projects and Enabling Sciences.

**Predictive Sciences**: Predictive Sciences is at the core of the OSDD project since its launch in the year 2008. The first delivery of the OSDD predictive sciences group was the semantic web-based collaborative platform, SysBorg2.0, which is a unique portal for managing distributed communities. It manages 7900 members from 130 countries with over 238 projects and 400 lab notebook entries.

Can ‘crowd sourcing’ impact ‘drug discovery’? This question was successfully answered through an elegantly designed project. In the past five years, the predictive sciences group has trained over 2000 students across the country on genome annotation protocols to build cheminformatics models for predicting anti-tubercular and anti-malarial compounds.

This was done through the innovative design and implementation of the Connect to Decode Project. This has led to interactive Platforms for community involvement, data sharing, project sharing and approvals – SysBorg2.0, as well as Platforms for sharing compound and associated biological data – OSDDChem, OSDDChemDesign. (These platforms can be accessed through the OSDD website.)

The next step up was augmenting this network with relevant information to facilitate discovery programmes, by release of a large number of data resources and computational models from the OSDD community members. The approach of the predictive sciences group is to create a Systems Level Platform for Drug Discovery. At each stage, OSDD has collaborated with the best global experts.

To give a few examples, OSDD collaborated with the Systems Biology Institute, Japan, on developing platforms for metabolic modeling, cheminformatics models with Indiana University, USA, prediction of off-target binding to reduce toxicity with Cambridge University, etc. More recently, OSDD entered into a MoU with the Royal Society of Chemistry on various aspects of designing Cheminformatics projects towards drug discovery and development.

**Discovery Projects**: Robust drug discovery projects have been built that have the ability to deliver novel ‘hits and leads’ from the target-based and whole cell-based approach. These projects have been built harnessing the creativity and innovation of academic research and building in the missing ‘gaps’ that are required for the translation.

The projects pursue novel hypothesis such as ‘targeting multiple targets of pathway with a single inhibitor’ (FAACL/FAAL project and sigma factors-RNA polymerase interaction) or targeting novel pathways or proteins (Ribosome biogenesis and DATIN) project. Novel approaches like ‘phage based therapy’ which has the potential ability to decrease the duration of therapy are also being pursued.

Several target-based programmes like DapA/B, Gmu, NAD Ligase and MAP are progressing aided by structure-based strategy. Significantly, these projects have all been oriented towards drug discovery with appropriate deliverables, time lines and ‘Go/No Go’ decision points. Ability to provide support to various ‘hit to lead’ optimization projects like CDRI 830 and LAMS project has been built in.

Targets like multiple sigma factors and Mur enzyme pathway that have been predicted from systems biology have been converted into drug discovery projects and are being executed.

**Enabling Sciences**: This is the ability to take the predictions from the robust systems level understanding of Mtb to implementable drug discovery projects.

Firstly, the ability to validate the essentiality to Mtb survival by knock out and/or knock down for the drug targets predicted by systems level analysis of Mtb has been created at academic labs and Contract Research Organization (CRO) which will pave way for building new drug discovery programs.

Secondly, platforms for early drug discovery have been developed which include various biological assays and
compound screening. Clone repository of Mtb genes (SASTRA University) and repository of clinical strains (at Premas Biotech) has been built. Cloning, expression, purification and optimization of biochemical assays and microbiology assays for determination of Minimum Inhibitor Concentration (MICs) has been set up involving various academic labs and specific CROs that have been hired for this purpose.

National Molecule Bank (MolBank), the central small molecule storage facility at CSIR-IICT, presently has a capacity to maintain up to 1.5 million small molecules. In partnership with MolBank over the last few years we have been able to encourage the deposition of novel chemical entities by over 80 PIs located at institutes all across India into this centralized chemical repository. This has enabled the creation of a diverse compound library that has expanded our drug discovery efforts into chemical space not traditionally covered by commercial compound libraries.

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MolBank plays a central role in the drug discovery process by providing 1) centralized and systematic collection and storage of compounds from labs all over India, 2) facilities for retrieval and standardized plating of selected compounds from the growing library, and 3) the ability to package and ship compounds to laboratories across India for biological testing according to technical specifications. This compound management platform has been developed and streamlined at MolBank in partnership with OSDD and facilitates drug discovery across the OSDD community.

So far, under whole cell screening (WCS) about 8500 compounds have been...
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OSDD’s discovery programmes. We envisage to build up this translational platform in OSDD.

The pre-clinical studies on candidates obtained from our pipeline will be carried out by us with appropriate partners or CROs. Those that show promise will be progressed into the clinical trials. We have started work towards building a ‘multiple clinical trial platform’.

OSDD has piloted the necessary documentation and discussion through the entire regulatory protocols to obtain permission to carry out the trials in India. A public funded institution under the Ministry of Health, National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi has been identified as the investigator, which is obtaining appropriate ethical clearances. The National Institute of Research in Tuberculosis (NIRRT) Chennai, an ICMR institute, is the partner institute to provide clinical science inputs. Permission to carry out the trials has been obtained recently. This programme brings in an otherwise unavailable clinical trial management competence in public sector.

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Dr Geetha Veni Rayasam is a scientist associated with Open Source Drug Discovery, Anusandhan Bhavan, CSIR, 2, Rafi Marg, New Delhi-110001; Email: grrayasam@csir.res.in

Dr Tanjore S. Balagangesh is Head of the Open Source Drug Discovery Research Unit, Indian Institute of Science, Bangalore, Karnataka