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CSIR Led Team India Consortium with Global Partnerships
for
Affordable Healthcare for All

Proposal Submitted before
‘WHO Expert Working Group on R&D Financing’

“OPEN SOURCE DRUG DISCOVERY”
AN OPEN COLLABORATIVE DRUG DISCOVERY MODEL FOR TUBERCULOSIS

Submitted by

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INTRODUCTION

Government of India has launched the Open Source Drug Discovery (OSDD) initiative, led by Council of Scientific and Industrial Research (CSIR), as an initiative for affordable healthcare. CSIR is one of the largest publicly funded research organizations in the world. OSDD is designed as a CSIR led Team India consortium with global partnerships. Tuberculosis (TB) is OSDD’s first target for drug discovery due to its high incidence and mortality in India and other developing countries.

There has been no major breakthrough which can substitute the lengthy DOTS therapy for tuberculosis. Pharmaceutical industry has made a commendable contribution to the discovery of drugs for several diseases. Some major research based pharmaceutical companies have made efforts at TB drug discovery. The market size and inability of patients to pay for costly drugs discourages substantial investment in Tuberculosis. The editorial of Nature of 25 June 2009 (Nature 459, 1034), quoted Anthony Fauci, Head of the US National Institute of Allergy and Infectious Diseases as stating that generations of advances in research and technology have bypassed TB research. The same editorial has quoted Margaret Chan, Head of the World Health Organization, as stating that the field of TB research has been too isolated and inward-looking. OSDD tries to bring research on Mycobacterium tuberculosis to the open sky so that researches across the world can share and collaborate, thereby bringing many eyeballs to the problem. The lack of participation of brilliant young people from the academia in present drug discovery model, fails to tap the resources of brilliant minds to address this problem. In order to tackle these challenges, OSDD tries to collectively aggregate the skills of researchers in academia, research laboratories, industry and elsewhere for a collaborative, sustained and coordinated attempt at drug discovery for tuberculosis.

CSIR has set-up a comprehensive portal for Open Source Drug Discovery (OSDD) www.osdd.net. Currently more than 1500 registered participants are working on more than 100 projects posted online. These participants are from 31 countries. OSDD harnesses the competencies of private sector through public private partnerships in an open mode. All research results are published on the website, whether done in the academia, industry, public sector laboratories or by collaborating researchers.

The new drug that is likely to come out of the drug discovery process will be made available as a ‘generic’ molecule, free of intellectual property (IP) constraints for the industry to manufacture and distribute anywhere in the world, thereby ensuring that the prices are affordable.
OBJECTIVES AND CONCEPTS

OBJECTIVES

- To establish a novel open source platform, computational and experimental, to discover drugs for tuberculosis, affordable to the people of developing world ([www.osdd.net](http://www.osdd.net) set up and various collaborations are in place).
- To create a CSIR-led Team India Consortium with international collaboration to lead open source drug discovery programme.
- To develop a novel comprehensive systems biology approach to generate a comprehensive interaction map of the pathogen (ongoing).
- To discover and develop of New Chemical Entity (NCEs) for *Mycobacterium tuberculosis* including drug resistant and latent tuberculosis. (First phase activity being carried out.)
- In the second phase, clinical trials will be undertaken.
- To make available the new drug as a ‘generic’ drug without IP constraints, available in the open, so that the industry anywhere in the world could manufacture and distribute, reaching the drug to the patients at affordable prices.

CONCEPTS

The following are the tenets of this proposal:

- Drug at an affordable cost is the right of all. Affordable healthcare is the motto of OSDD.
- OSDD encourages and supports ideas and scientific projects from the scientists researchers and even students in an open source mode. In addition, OSDD has developed a micro-attribution system through which credit points will be given to contributors based on the value of their contributions. The involvement of universities with a good source of talent pool will be secured. The involvement of private sector is secured to participate in “open source” initiative under Private-Public partnership mode. The combined effort of all these players is likely to significantly optimize the cost and time of drug discovery significantly.
• The major open source initiatives that have caused revolution are the World Wide Web (www), Open Source Operating System (Linux), and Human Genome Sequence. The Open Source Operating System is gaining wide acceptance globally and is showing accelerated growth. Present IT infrastructure, connectivity and high throughput analytical capability makes OSDD possible.

• During the current decade models of out-sourcing research to Contract Research Organizations have become a factor in drug discovery process enabling even virtual pharmas. The model proposed by OSDD is similar to the virtual Pharma concept, but is also distinct in its concept to tap the resources in academia, public sector research organizations, private sector and other interested researchers with high talent, thereby plugging a talent gap. Drug discovery for tuberculosis, therefore, moves out of interiors of pharmaceutical companies to open sky to enable young generation to participate globally. This model is replicable and is capable of ensuring health security in the developing world, particularly for Type II and Type III diseases.

• Issues like IPR protection and confidentiality which significantly enhances the cost of drug discovery is approached in a knowledge sharing mode. The contributions are protected through a ‘ClickWrap’ agreement against misappropriation. Each contribution is time and login stamped to ensure quantitative evaluation and micro-attribution.

• NCE will be free of intellectual property encumbrances (generic) as soon as it is discovered/developed. The cost of clinical trials will be met by OSDD consortium. These generic molecules which are approved as drugs can be used by any company to manufacture the drug. The competition at the market place will keep the drug prices at affordable levels.

OPERATIONAL METHODOLOGY

The drug discovery process in OSDD project has been divided into ten work-packages.

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<tr>
<th>Work Package</th>
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Phase I – WP 1 to 8 (Duration 2008-2012)
Phase II – WP 9 & 10 (Duration 2012-2017)

It is not essential for the work packages to be taken up in a serial manner. OSDD approach facilitates parallel processing of the work packages allowing those having skills in the respective work packages to address the respective challenges. This multi-pronged approach ensures optimal utilization of cost and resources.

**OVERVIEW OF WORK PACKAGES**

**Work Package 1 – Identification of Targets** – (all non toxic sites to humans)- Uses computational activities including Systems Biology research for identification of potential drug targets. This package enables participation of academia, institutions and industries with strong inclination towards Open Source.

**Work Package 2 - Expression of targets and assay development**- This involves expression of potential drug targets and development of assays. This work package brings in the true concept of sharing experimental results and experience in open source.

**Work Package 3 - Screening of compounds** – involves the use of specific assays developed for different targets to screen large chemical compound libraries in a high throughput manner or small group of compounds synthesized on the basis of rational drug design to obtain potential hits.

**Work Package 4- in silico docking** of hits to the target and identification of potential sites on the hit compounds for synthesis of analogs with a view to increase potency and rule out toxicity.

**Work Package 5- Micro array gene expression for human cells and tissues with the best inhibitors** - This package identifies compounds with higher binding affinity for the target but do not alter the expression profile of host cell significantly compared to the native un-intervened state.

**Work Package 6- Medicinal chemistry** - Synthesis of compounds to obtain leads with the desired activity and better drug-like characteristics.

**Work Package 7- Lead Optimization**- Optimization of lead compounds to obtain ones that do not alter the gene expression profile in the host.

**Work Package 8- Proteomics based lead affinity column to check for human cellular protein binding** - Creation of a lead affinity column to check for Human Cellular protein binding (side effect) using proteomics.

**Work Package 9- Pre-Clinical Toxicity of the Lead Compounds**- in order to develop a pharmacological profile of the investigational drug.

**Work Package 10 - Clinical Trials.**
**METHODOLOGY**

The activities under these work packages are implemented as projects. These projects are posted on the OSDD portal. OSDD envisages participation of pharmaceutical industry and Contract Research Organizations in addition to participation of academia and research organizations. All research results are uploaded in real time. Credits are attributed to contributors. The project ensures smooth interaction and transition of ‘drylab’, ‘wetlab’, medicinal chemistry and other experiments in a coordinated fashion. A Click Wrap license protects against misappropriation.

**PPPs in Open Source Model**

OSDD program is spearheaded by CSIR, one of the largest publicly funded research organizations in the world. CSIR has an admirable track record in drug discovery. OSDD program envisages to optimizing competencies of the public sector with that of a private sector, through Public Private Partnership (PPP) model. The private partner will be compensated for the research expenses and the results of the research will be shared with the open source community through the portal.

**MANAGEMENT METHODOLOGY**

OSDD approaches the science of drug discovery in a carefully planned, yet decentralized manner. The scientific activity is closely monitored by experienced scientists. The Chief Mentor is Prof. S. K. Brahmachari, Director General of CSIR, a world renowned scientist. Scientific luminaries like, Prof. M Vijayan, President, Indian National Science Academy, Dr. V M Katoch Director General, Indian Council of Medical Research (ICMR), Dr. N.K. Ganguli, Former DG, ICMR, are Mentors guiding the science. Each project is managed by a Principal Investigator (PI) with appropriate competence. They manage the scientific activities online by aggregating the skills available within the OSDD
community and that of partners. The projects which require funding are reviewed online and funded in an open and transparent manner. The ongoing projects are monitored by a competent group of scientists as well as the OSDD community. The Project Director of the project coordinates the overall activity.

**FUNDING**

Government of India (GOI) has committed $46 million towards this project, out of which $12 million has already been released as a first phase. OSDD proposes to raise equivalent amount of funding from multilateral/bilateral agencies and philanthropic organizations.

The fund from GOI is currently being utilized to finance ongoing projects within India. OSDD is also tapping funds available under bilateral scientific agreements. Along with Systems Biology Institute (SBI) of Japan, it has submitted a Joint Proposal to develop a collaborative, community-wide communication initiative for open-flow biology under the bilateral agreement between India and Japan called *Strategic Japanese-Indian Cooperative Programme on “Multidisciplinary Research Field, which combines Information and Communications Technology with Other Fields”*. Dr. Hiroaki Kitano, Director SBI, is the PI of this project along with Prof. S. K. Brahmachari, Chief Mentor OSDD.

To address the TB challenge OSDD needs to bring together the best researchers and laboratories across the world. The funds are required from multilateral organizations/bilateral programs to support research activities arising out of international participation from research organizations, universities and pharmaceutical companies situated abroad as the funds from GOI can only be utilized for funding research abroad. This proposal to WHO is tailored against this backdrop.

OSDD has raised contributions from the Philanthropic organizations like The Lemelson Foundation which supports Cambia, Australia, to develop a patent landscape of tuberculosis on OSDD. It plans to
raise an equivalent amount from other philanthropic organizations, to match the contribution of GOI and multilateral / bilateral agencies.

**REWARDS AND PRIZES TO INCENTIVIZE DISCOVERY**

OSDD proposes to announce rewards and incentives for solutions provided for the complex drug discovery challenges posted as projects on the OSDD portal. For this purpose a micro-attribution system has been developed to attribute each contribution. These will be converted into credit points, wherever applicable. Credit points can be accumulated to claim rewards. A private hotel chain based in India has offered free stay in a holiday home near a bird sanctuary to reward the highest contributors on the OSDD portal during a month. Specific prizes like iPods, mobile phones, laptops, etc will be announced to attract young minds to solve complex problems.

**FUNDING OF PROJECTS / MONITORING OF UTILIZATION**

OSDD utilizes the funds from GOI to fund projects proposed online. The projects are to be focused on drug discovery for tuberculosis and should have clear deliverables. All projects requiring funds from OSDD are to be posted online. Such projects are subject to a transparent online review by OSDD community and open peer review by a selected team of scientists. Their comments are available online. The projects recommended through the open peer review get funded and the deliverables are also known to the community. The projects which have received funding are required to post the research results on an ongoing manner and these results are reviewed by the community.

**WORK DONE SO FAR**

OSDD was launched on 15th September 2008. Currently it has about 1600 registered participants from nearly 30 countries. This has enabled global exchange of scientific information on tuberculosis through the OSDD portal.

The portal has about 110 ongoing projects, some of which addresses complex scientific challenges on drug discovery for tuberculosis. The results of the projects are posted in real-time on the portal in an open electronic lab note book which is for community-wide review.

The OSDD community has identified more than 60 potential drug targets of *Mycobacterium tuberculosis*. Seven targets are being actively followed-up for onward investigation by highly competent PIs. An international publication has already come out of the work of OSDD scientists arising out of virtual collaboration (PMID: 19683474).

OSDD portal has made online peer-review of scientific projects. Involved discussions on complex scientific problems are available on the portal. OSDD portal is a pioneer in the online review of research projects for funding. This has made the funding process highly transparent and accountable.
to the whole community. It also enables speedy deployment of funds to deserving projects. In almost all cases, funds have been released to projects which have received favorable reviews within six months of uploading the same.

OSDD has demonstrated the power of open online collaboration. A project on Pathway Annotation of *Mycobacterium tuberculosis* annotated more than six hundred genes in less than six months with collaborators from different parts of India, while KEGG took ten years to annotate nearly twelve hundred genes.

OSDD has put in place a number of private-public partnerships which includes reputed organizations such as Sun Microsystems, M/s. Infosys Ltd, TCG LifeSciences, ChemBiotek, Biozeen, CellWorks and many others.

OSDD has created a number of online resources which includes SysBorg (the collaborative annotation portal), Computational Resources for Drug Discovery (CRDD), Tbrowse (integrative genomics map of *Mycobacterium*), OSDDpub (archive of tuberculosis publications), pulmonet (social networking for clinicians), etc.

OSDD is collaborating with ten universities and about 20 colleges across India in its activities. A group in University of California, San Francisco is also collaborating on a project. The Global Research Alliance (GRA) which has conglomeration of nine CSIR-like research organizations is a partner of OSDD. CSIRO-Australia has proposed to join OSDD with its skill in Fragment-based drug discovery.

### DELIVERABLES

#### PHASE I (2008 - 2012)
1. Web-based collaborative platform for drug discovery
2. Tools for drug discovery
3. Identification and validation of novel targets
4. Finding new leads and optimizing existing molecules
5. Development of NCE

#### PHASE II (2012 – 2017)
6. Pre-clinical trials
7. NCE to be made available as Generic as soon as it is discovered
8. Clinical trials
**SPIN-OFFS**

(i) Enrichment of scientific expertise through continuous exchange of ideas through the OSDD portal.

(ii) Human resource development in the area of drug discovery, transcriptomics, proteomics, integrative biology, pharmacoinformatics, Systems Biology etc.

(iii) OSDD has a ‘women scientists program’ to encourage women scientists. Compensation is provided for their work from home.

(iv) Generation of a large of number of computational tools for drug discovery.

(v) Private enterprises could benefit in the same way that ‘RedHat’ has emerged in open source software.

(vi) Bringing in the spirit of openness and collaboration in scientific discovery and drug development.

(vii) Publications of high quality research papers in peer-reviewed scientific journals.

(viii) OSDD enables students to participate in actual drug discovery related experiments kindling their enthusiasm for science. Drug discovery process benefits from their fresh insights and enthusiasm.

**IN SUMMATION**

OSDD has made a promising start and has made inroads into the complex world of *Mycobacterium* in its very first year. With the strength it has achieved in a year, it is likely that it will deliver a New Chemical Entity (NCE) which will be a cure for tuberculosis. This is a promising platform which can be extended to other diseases in the Type II and Type III category for affordable healthcare. WHO’s endorsement of this project and its active participation will give a boost to this collaborative and coordinated drug discovery project on tuberculosis.

**REQUEST FOR FUNDING**

*Mycobacterium tuberculosis* is a complex organism which has evaded significant inroads into drug discovery since the development of DOTS therapy. Many universities, research institutions and even established pharmaceutical companies, such as, Johnson & Johnson, Novartis, AstraZeneca and others, have made significant efforts at discovering a new drug. Yet, as the Nature editorial lamented (*Nature* 459, 1034 (25 June 2009)), generations of advances in research and technology have bypassed TB research. The editorial carries the call of Margaret Chan, Head of the World Health Organization, for an alternative to the isolated and inward-looking approaches practiced so far. OSDD
model brings TB research into the open as contrasted to the closed door approaches practiced so far. Meeting the challenge of *Mycobacterium tuberculosis* requires bringing together an international collaboration of the best minds of the field, including pharmaceutical companies, research organizations, universities, private entities and brilliant minds across the world, for a focused and targeted attack on this organism. The open source movement was successful in software, as large numbers of volunteers – “many eyeballs” – looked at the code, which was a great way to find bugs. The OSDD approach brings many eyeballs together on *Mycobacterium*.

As per the OSDD model, the NCE will become Generic as soon as it is discovered/developed. The cost of clinical trials will be met by OSDD consortium. These generic molecules which are approved as drugs can be used by any company to manufacture the drug in any part of the world. The competition at the market place will keep the drug prices at affordable levels.

The OSDD has an interesting model of funding drug discovery with seed fund committed by the Government of India and equivalent amount to be raised from multilateral/bilateral science donors and philanthropic agencies/individual donors. The seed fund committed by the Government of India has kick started the project and has drawn in about 1600 participants from 30 countries, already facilitating an unprecedented international collaborative effort against *Mycobacterium*. The funding from the Government of India can be deployed only for projects in India. For a successful attack on *Mycobacterium*, OSDD needs to bring together universities, research organizations and pharmaceutical companies across the world on scientific projects directed at drug discovery for tuberculosis. Funding is needed for carrying out research in other countries. OSDD seeks the assistance of WHO to fund its cross border projects focused on TB drug discovery. It is requested that WHO commit an amount which is equivalent to the commitment made by the Government of India towards this project. The release of funds may be in phases. In the first phase an amount equivalent of $12 million, which Government of India has released, may be released by WHO.

OSDD has a transparent mechanism for selecting the science projects for funding. It will co-opt reviewers from WHO or its nominated agencies in review of projects funded using WHO funds.