CSIR-Open Source Drug Discovery

OSDD Foundation Day: Brief Report

15th-17th September 2014

As a part of the OSDD Foundation Day various activities were organized at OSDD Unit at CSIR Headquarters, New Delhi during 15th-17th September 2014. In order to mark the OSDD foundation day and completion of six successful years of operation, Dr. Vijayaraghavan Secretary, DST was invited to deliver the OSDD Foundation Day Address on 15th September. Following three activities were carried out under the banner of OSDD Foundation Day.

a) 15 September 2014: Overview of OSDD and TCOF Review

Brief Report

The meeting started with Dr. Sarala Balachandran, Project Director, CSIR-OSDD welcoming the participants and inviting Dr. P.S Ahuja, Director General, CSIR to address the PIs. Speaking on the occasion, Dr. Ahuja drew attention to the fact that TB is a disease with major connotation with socio-economic status and CSIR-OSDD in this context is playing a major role in exploring simpler and affordable solutions. Speaking about the PA-824 molecule that would soon be entering the clinical trials, in collaboration with Global Tb-Alliance, Dr. Ahuja appreciated that the reverent spirit of collaboration, which forms the basis of OSDD has been kept up throughout the process. Dr. Ahuja pointed out that the OSDD modes operandi of networking institutes including colleges to arrive at a cost effective solution for TB is indeed novel and praiseworthy.

During the meeting Dr. Sarala Balachandran presented a summary of OSDD activities and elaborated on the work that was being carried out under different categories as follows.

Ongoing in-silico work being done under Discovery category

- Training of undergraduate students on docking and molecular modeling
- Target identification in Mtb
- Collaboration with Cambridge University, England
- Development of Molecular Property Diagnostic Suite (MPDS) with the Royal Society of Chemistry (RSC)

Ongoing activities under synthesis and screening

- OSDD is involved in diverse compound library synthesis. Approximately 1200 compounds have been synthesized which has been stored in the National Mol Bank at IICT.
- Whole cell Screening Activities

- Establishment of screening platform and compound library screening against *M semgmatis* at IICT
- Screened against Mycobacterium tuberculosis in collaboration with CRO
- Hit Optimization Programs
- Establishment of Assay Development and Target Based Screening in collaboration with CRO
- Initiation of OSDD-GSK Tress Cantos collaboration
- Work on newly identified scaffolds

Speaking on the ongoing developmental activities of OSDD with regards to PaMz, Dr. Balachandran stated that CSIR-OSDD has entered into an agreement with TB Alliance, US according to which CSIR has the right to take the new drug regimen for development and price it in the market within the country. Dr. Balachandran also elaborated on the work done since April 2014 in the context of clinical trials. This covers

- Repackaging of IP through a company selected though tender
- Insurance cover of trial accomplished via open tender
- Financial support provided to NITRD on 6th Aug, 2014
- Finalization of SOPs of clinical trials with NITRD
- Planning of IM
- CTRI registration completed.

Dr. Balachandran stated that the patient screening for recruitments in clinical trials is expected to start by beginning of November 2014 and CSIR-OSDD is currently discussing with NIRT (TRC), Chennai to be a second centre for the trial.

TCOF Review

Reviewers

1. Dr T. Balganesh
2. Dr Sarala Balachandran
3. Dr Andrew Lynn
4. Dr Jaleel UC
5. Dr Swati Subodh
6. Dr Urmi Bajpai

Details of the Review:

During the meeting the Review Committee, which consisted of above members reviewed the progress and status of work being carried out under the TATA fellowship. The committee discussed about various achievements under TCOF and the existing challenges.

1) Streamlining a procedure to speed up the allocation and award of TATA fellowships to selected students was stressed upon. The possibility of direct distribution of fellowship by TATA trust was discussed in detail. In case of non-availability of the option, use of 10% of the total amount granted by TATA for administrative expenditure was proposed. The change of fellowship distribution point to SID, IISc, Bangalore or IICT Hyderabad was also discussed.
2) It was decided to take permission from TATA to alter the project based on the recommendations of TATA fellowship committee, without affecting the overall idea of the project.
3) It was decided to increase the amount of fellowship for PhD scholars , Post PhDs and MTech based on the recommendations of the PI subject to approval from TATAs
4) It was decided to extend the time period of selected TCOS based on their performance and recommendations of the PI subject to approval from TATAs
5) There is a provision for taking guest houses for students at Bangalore. Since the advance to be paid for the houses are not included in the project, that facility was not availed off till date. So can we include the rent amount to the students so that we can reduce the burden of taking guest houses and administrating them subject to approval from TATAs

b) 16th September- Scientific Review

Participants:

1. Dr. T Balganesh
2. Dr. Sarala Balchandran
3. Dr. Geetha Vani Rayasam
4. Dr. Urmi Bajpai
5. Dr. Swati Subodh
6. Dr. Sidharath Chopra
7. Dr. Madhavan Nampoothri

In order to review the status of funded projects and deliberate on the future course of action, CSIR-OSDD conducts an annual review meeting every year. The annual review meeting is usually conducted on the CSIR-OSDD Foundation day on 15th September and PIs from all the collaborating institutions are invited to present their work. However given the delay in the approval and allocation of funds for the financial year 2014-15, the OSDD annual review meeting of 2014 involving all the PI's which was to be conducted in September has been postponed by 6 months. The decision has been made in consultation with all the concerned PIs. However short scientific reviews of four ongoing projects which had completed one year were conducted on 16th September 2014 in association with the CSIR-OSDD Foundation Day. The four projects which were reviewed for their progress where:

1) Mtb Mur Pathway enzymes: Potential candidates for multi-targeted drug therapy: Dr Urmi Bajpai
2) Identification of TB drug response genetic markers, Dr Swati Subodh
3) Determination of Mode of Action (MOA) of drugs against Mtb: Dr Siddharth Chopra
4) Investigation on bioactive molecules inhibiting betalactamases and methionine aminopeptidases of Mycobacterium tuberculosis: Dr Madhavan Nampoothiri

Project Reviews in Brief

1) **Project : Mtb Mur Pathway enzymes: Potential candidates for multi-targeted drug therapy**
   Principle Investigator: Dr Urmi Bajpai
   Institute: Acharya Narendra Dev College

The presentation highlighted the progress achieved in the project so far. All the Mur pathway enzymes (A-F) of Mtb have been cloned. The optimization with respect to expression, purification and optimization of individual proteins of the pathway was presented. All proteins with the exception of D and F were purified by Ni-NTA affinity chromatography. Mur D and F were purified by MBP affinity chromatography. The sequential coupled assays were developed for all the proteins as many of the intermediate substrates are not easily available commercially. Optimization of each of the proteins was described in detail. Finally optimization of one pot assay involving all the mur pathway enzymes with respect to incubation period, conc. of ATP and conc.

of each enzyme was presented. Inhibition data with Feglymycin and D cyclo serine was described. Future work would involve further optimization of one pot assay and screening for novel inhibitors.

Recommendations

- Conducting control experiments in absence of Magnesium that may decrease the non-specific ATPase activity was suggested.
- It was also suggested that IC50 for Feglymycin be determined for Mur A and C.

2) Project : Identification of TB drug response genetic markers:

Principle Investigator: Dr Swati Subodh
Institute: CSIR-OSDD

The experimental design, objectives and results from the pilot data was presented. 38 patients satisfying the inclusion criteria were enrolled in the pilot study. Spoligotyping revealed 20 different patterns and majority were Delhi clade. DNA extraction from Mtb cultures was optimized. Optimization of RNA is in progress along with Rea Matrix. Mtb DNA was profiled for Drug associated mutations in a few strains. Estimation of drugs in plasma needs standardization with respect to stability of drugs in plasma shipped in cold chain. Various databases and parameters used in identification of DMETs that are involved in TB drug metabolism. SNPS that were polymorphic and associated with function were prioritized and those that have been reported to be variable in Indian population were shortlisted. It was proposed that finally about 150 such SNPS would be used in the study. The next phase of the project ie Phase I design was explained. The new design would include collection and examination of samples from patients only at 6 months and 5 months after initiation of treatment, in smear positive and smear negative patients respectively. About 50 patients each from the groups that are fast responders (smear negative at 2 months), slow responders (smear positive at 2 months but negative at 6 months) and non responders (smear positive at both 2 and 6 months). The DNA and RNA extraction for the studies would be done from sputum collected from patients. It was proposed that multiple hospitals and MCD hospital patients may be used to hasten the patient's recruitment.

3) **Project: Determination of Mode of Action (MOA) of drugs against Mtb**

Principle Investigator: Dr Siddharth Chopra
Institute: CSIR-CDRI

Progress made in the project so far was presented. It was highlighted that the MIC conditions were standardized and MIC of CDRI-830 against M. bovis BCG was determined to be 10 µg/ml. Isolation of resistant mutants of BCG against CDRI-830 was attempted. However, no stable mutant of CDRI 830 was isolated suggesting that CDRI-830 perhaps inhibited multiple drug targets in Mycobacteria.

Recommendations

It was recommended that BM212 analogs synthesized by Dr Srinivasa Reddy from NCL be characterized for mode of action by raising mutants in BCG and sequencing.

4) **Project: Investigation on bioactive molecules inhibiting betalactamases and methionine aminopeptidases of *Mycobacterium tuberculosis***
Principle Investigator: Dr Madhavan Nampoothiri
Institute: CSIR-NIIST

Cloning and expression of MAP-A and B from Mtb was presented. Low yield from MAP A was reported owing to poor solubility of the protein. Analysis of the M. tuberculosis H37Rv genome revealed that Rv2068c (blaC), Rv0406c and Rv3677c gene products exhibited beta lactamases activity. Expression and activity of beta lactamase C and blaC like protein was presented. It was reported that 200 bioactives were screened, out of which 41 were made from microbes isolated in NIIST. The microbes were identified by 16S rRNA amplification and sequencing.

Recommendations

- It was recommended that the work on beta lactamases be prioritized over MAP A & B.
- Bioactive fractions identified and characterized to be shared with Dr Urmi Bajpai for the purpose of screening the fractions against Mur pathway.

c) 17th September - OSDD-THSTI meeting

As a step towards strengthening the collaborative network of CSIR-OSDD in and around National Capital Region, CSIR-OSDD held a meeting with Translational Health Science and Technology Institute (THSTI), Haryana on 17th September 2014. The meeting was attending by four leading researchers- Dr. Ramandeep Singh, Dr. Amit Kumar Pandey, Dr. Krishnamohan Atmakuri and Dr. Nisheeth Agrawal from THSTI and the core group of CSIR-OSDD unit. Discussions were undertaken pertaining to furthering collaborative translational research in the area of drug discovery for neglected diseases.

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