R&D Demonstration Project

R&D demonstration projects were selected as per the Executive Board decision EB134(5) following review by the former Chair and Vice-Chair of the CEWG

1. Title of the project:
 Exploiting the Pathogen Box: an International Open Source collaboration to accelerate drug development in addressing diseases of poverty

2. Proponent/s of the project:
 Medicines for Malaria Venture

3. Project executive summary:

The “Pathogen Box” is a MMV led project that has received 3 years of funding from the Bill & Melinda Gates' Foundation. The Pathogen Box (PB) has made molecules pre-screened by MMV and its partners available to researchers to apply to their areas of disease investigation. From an initial library of some 4 million compounds, MMV has made available 400 of the most promising, free-of-charge to researchers and will publish full ADMET in vitro characterization of compounds as well as oral mouse exposure data. Consequently there will be an unprecedented wealth of compound data to aid researchers and drug hunters. The PB was launched in December 2015.

The Medicines for Malaria Venture (MMV)'s Demonstration Project “Exploiting the Pathogen Box: an international open source collaboration to accelerate drug development in addressing diseases of poverty” has the aim to maximize and exploit the richness from the PB so as to maintain momentum towards discovery of drugs against a range of neglected diseases\(^1\). The project is being run in an Open Source mode in collaboration with global partners so as to benefit the research and drug discovery communities and enhance the likelihood of products ultimately being delivered. All the data will be made publicly available as early as possible through open access sites such as ChEMBL. The project intends to help build sustainable capacity in disease endemic countries. It also delinks the price of the final product from the cost of R&D.

In addition Challenge Grants will be awarded (Year 2 to Year 5) to scientists based in Endemic Regions to further exploit the Pathogen Box. These grants will help to build capacity in endemic regions and will be awarded via an annual Call for Proposals managed by MMV.

The specific objectives for the project over a 5-year period are as follows:

1. Identify the mechanisms of resistance and modes of action on up to 25 Pathogen Box compounds
2. To deliver, in open source collaboration, up to 25 robust “hit” series against relevant pathogens
3. Award 10 Challenge Grants to Endemic Region Scientists each year (Year 2 to Year 5)

Thus, the proposal leverages considerable current investment to deliver series that will be the foundation of future drug discovery projects for neglected diseases.

4. Innovative aspects of the project

Due to its open source nature, this project will deliver greater reach and impact across the entire neglected disease area with the potential to transform Pathogen Box compounds into high quality drug discovery projects. With its innovative approach, this project has the potential to be a very cost-effective way of spurring generation of new series of compounds. Linking the Pathogen Box compounds to endemic region scientists through the Challenge Grants will further aid capacity building for neglected disease drug discovery.

\(^1\) Malaria, Mycobacterium Tuberculosis, Leishmaniasis, Cryptosporidiosis, Chagas, Human African Trypanosomiasis, Lymphatic filariasis, Onchocerciasis, Schistosomiasis and other orphan or neglected tropical infectious diseases
5. The current status of the project

MMV has been awarded with US$ 1 360 000 through letter of Agreement of 6th August 2015, which corresponds to Year 1 budget. The project is in the implementation phase and started in August 2015.

6. Progress towards activities since the start of the project

Year 1 Goals

1) Hit expansion around 10 compounds to deliver 5 new robust series for further drug discovery optimization – focused on at least 2 different pathogens
   • Contracts arranged and chemistry ongoing at TCGLS (India), University of Ghana and University of Campinas (Brazil)
   • Structure Activity Relationships are being investigated for 16 chemical series – targeting malaria, kinetoplastids and tuberculosis
   • Encouraging improvements in activity observed in some chemical series
   • Further profiling of new compounds for biological activity and pharmacokinetic properties is in progress

2) Identify 5 new resistance mechanisms or targets
   • Screening of Pathogen Box malaria compounds against resistant strains outside the WHO funded project has identified potential biological targets and mechanisms of resistance – further work will be required within the Demonstration Project to investigate these findings.
   • Further identification of biological targets and resistance mechanisms is likely to expand in later years once further testing of Pathogen Box compounds has been completed

3) Endemic Region Challenge Grants – prepare for launch in Year 2
   • Plans in place to launch a call and to invite recipients to a drug discovery training workshop

7. The first-round award received/expected from WHO based on the recommendation of the Ad Hoc Committee

USD 1,360,000 received August 2015 (Year 1). MMV received 90% (US$ 1 224 000) of the funds after countersignature of the agreement. The remaining (US$ 136 000) (10%) will be received after acceptance of a satisfactory, final, detailed technical and financial report.

8. Future developments and challenges

The Pathogen Box compounds have been distributed to scientists around the world since early 2016. Once further data from this screening becomes available (anticipated to be 2H2016 onwards) an even wider degree of interactions and targeted pathogens are expected for this demonstration project. In addition to the regular investigation of new chemical classes a key milestone will be the launch of a call to Endemic Region scientists to enable grants to be provided and projects initiated in 3rd quarter 2016.

Funding of USD 2,460,000 per annum (from Year 2 to Year 5 with a total of USD 9,840,000) will be required to fully implement the goals of this demonstration project.

9. Other sources of support

MMV in kind contribution for the project. The Bill and Melinda Gates Foundation funded the Pathogen Box.

10. Any additional comments

None.