

The Pathogen Box: A Catalyst for Neglected Disease Drug Discovery

Benoît Laleu*, Thomas Spangenberg, Wesley Van Voorhis, Angelique Doy, Dylan Pillai, Andreas Verras, Joie Garfinkle, Jeremy Burrows, Timothy Wells, Paul Willis | Medicines for Malaria Venture, Switzerland | *laleub@mmv.org

Introduction

Modeled after the Malaria Box, the Pathogen Box contains 400 diverse drug-like molecules active against neglected diseases of interest.

Lessons learned from the Malaria Box

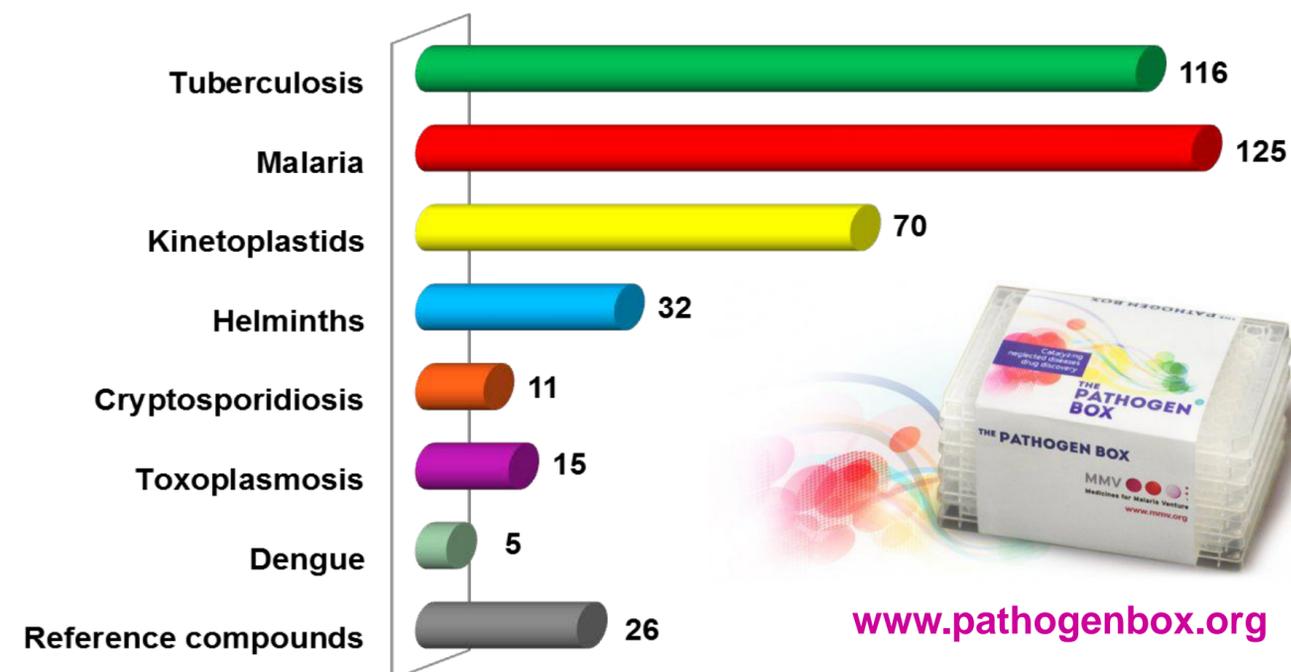
- Drug discovery in neglected diseases has limited access to new starting scaffolds and researchers want samples to test
- Early access to metabolism data and medicinal chemistry advice are key to progressing compounds
- Collaborations have been initiated with research teams in disease-endemic countries
- The quality of the Pathogen Box compounds was maximized by selecting almost exclusively drug-like compounds and adding some key reference compounds
- The Pathogen Box could have greater impact as compounds active against a number of pathogens were selected

Making the selection

To select the compounds for the Pathogen Box, the European Bioinformatics Institute's open access database (ChEMBL17) was analyzed and triaged to identify active chemotypes against the diseases of interest. In parallel, partners from many disease areas were approached to share their expertise and contribute quality hit molecules. This effort led to an initial list of 819 diverse chemotypes. In June 2014, a scientific selection committee composed of leading figures in medicinal chemistry reviewed the initial set of compounds to select 635 chemotypes termed as the "Beta set".

In addition to the Beta set, ~100 additional compounds were nominated from academic and pharma partners. A total of ~900 compounds (Beta set, intermediates, top-ups) were screened to confirm their biological activity before a final selection round to determine the 400 compounds that constitute the Pathogen Box.

Pathogen Box composition (number of compounds)



Diseases of interest / Composition

The Pathogen Box contains compounds with confirmed activity against either malaria, tuberculosis or a neglected diseases as prioritized by the WHO. Following a recommendation from the selection committee, 26 reference compounds were also included. The kinetoplastids set designates compounds active against at least in one of the associated diseases: Chagas disease, human African trypanosomiasis, cutaneous/visceral leishmaniasis. For diseases such as ascariasis or Buruli ulcer, it has not been possible to identify active molecules. It is hoped that screening the Pathogen Box may allow groups to find new hits for these and other neglected diseases.

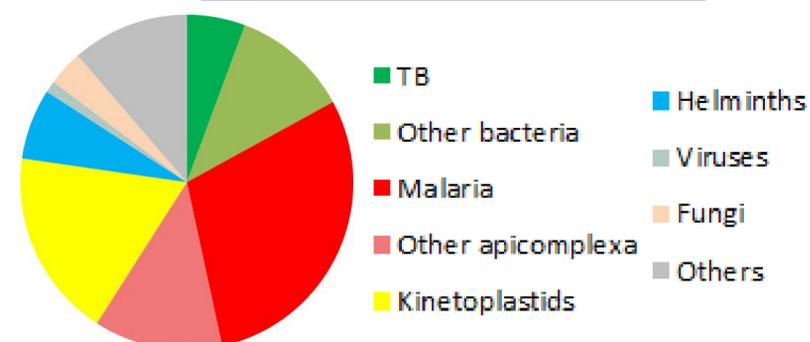
ADME/PK data are currently being collected for all the Pathogen Box compounds and will be provided on demand to the researchers.

Requesting and sharing the data

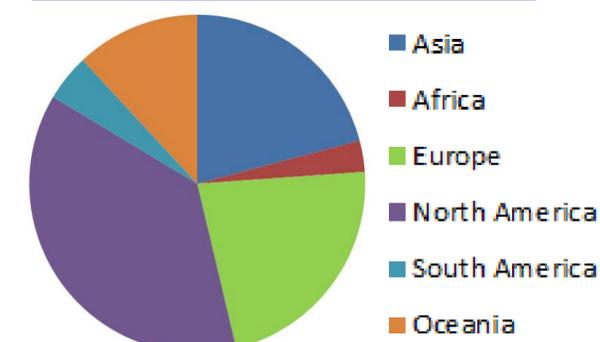
The Pathogen Box was launched in December 2015. It is available for free on request at <http://www.pathogenbox.org> and can be delivered to researchers across the world. In return, they are just asked to share any data generated, in the public domain within 2 years, creating an open and collaborative forum to catalyze neglected disease drug discovery.

~70 Pathogen Box copies have been shipped as of 24th March 2016 :

Distribution by diseases



Distribution by continents



Perspectives

The Pathogen Box is a unique set of valuable compounds with confirmed activity against a range of pathogens that will catalyze new medicinal chemistry programs and target identification in the field of neglected tropical diseases. Moreover, by making the Pathogen Box open access we aim to trigger a virtuous circle of open source drug discovery initiatives. Over time, we hope that this tool will help the research community to better understand the similarities and differences between diseases.

Acknowledgements

MMV would like to thank all collaborators for their support, in particular the Bill & Melinda Gates Foundation for their financial support.

References

- 1) Spangenberg T, Burrows JN, Kowalczyk P, McDonald S, Wells TN, Willis P. The open access malaria box: a drug discovery catalyst for neglected diseases. PLoS One. 2013 Jun 17;8(6):e62906.
- 2) Please visit our website <http://www.pathogenbox.org> for more information.