

Structural guidance for malaria and TB

By Kai-Jye Lou, Senior Writer

The **Structural Genomics Consortium** is spearheading the three-year Structure-guided Drug Discovery Consortium, which aims to bring pharma-quality medicinal chemistry capabilities to targets against malaria and tuberculosis. With a 3-year, \$5 million grant from the **Bill & Melinda Gates Foundation** and another \$10 million in supporting funds already available to its members, the drug discovery consortium will focus on projects that put early stage therapeutic assets in the hands of its key product development partners—**Medicines for Malaria Venture** and the **Global Alliance for TB Drug Development**.

Data generated under the new consortium also will be made publicly accessible to the broader scientific community.

"After AIDS, TB and malaria are the next two infectious diseases that have the highest global rates of mortality and morbidity," said Christopher Walpole, program director of the Structure-guided Drug Discovery Consortium (SDDC) at Structural Genomics Consortium (SGC) Toronto.

He noted that the SDDC steps in at a time when there is a new wave of targets in TB and malaria that have emerged from whole-cell screening and sequencing studies but there are only limited resources in pharma and academia to pursue drug discovery against them.

"SDDC will use its structural genomics pipelines to solve the 3D structures of as many of these high-value targets as possible and support collaborative, structure-based drug design programs while sharing information openly to minimize duplication of effort," Walpole told *SciBX*.

Current members of the consortium include SGC, the **Seattle Structural Genomics Center for Infectious Disease**, the **Midwest Center for Structural Genomics**, the **Center for Structural Genomics of Infectious Diseases**, the **TB Structural Genomics Consortium** and several academic drug discovery and pharmaceutical research groups.

The Gates Foundation is SDDC's main sponsor, and the foundation's \$5 million grant is designated specifically for the consortium's structure-guided medicinal chemistry efforts for generating lead molecules.

Walpole said the additional \$10 million in supporting funds stems from the funding that consortium members already have for their structural genomics work on TB and malaria targets. He said the structural genomics work carried out by the SDDC's members will

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Global Alliance for TB Drug Development

provide a crucial foundation for performing structure-guided drug discovery.

Most of the structural genomics centers and consortia under the SDDC have funding from the NIH.

From targets to leads

SDDC is working with its product development partners, sponsors and consultants who work in these disease spaces to sift through a portfolio of about 20–30 TB targets and 15 malaria targets.

"Our objective is to deliver pharma-quality early lead compounds and the associated scientific packages to our product development partners so they can optimize these leads to a clinical candidate within 12–18 months," Walpole told *SciBX*.

He added that the consortium will work with its product development partners to define project-specific criteria that would need to be satisfied before an asset is considered ready to be handed off.

Walpole said SDDC's objective is to deliver three such therapeutic asset packages to its partners over the next three years.

SDDC will deliver the compounds it discovers to the relevant product development partner at the end of the hit-to-lead stage of development.

The partner will then be responsible for lead optimization and setting up preclinical and clinical development programs.

With respect to IP, Walpole said SDDC intends to keep its work as open as possible.

"All new protein structures generated under the consortium will be deposited to the Protein Data Bank once they are available, and we intend to publish the small molecule hits we generate and make them publicly available," he told *SciBX*. "We don't expect to be restricted by IP before handing off an asset package to our

product development partners, but our partners may later opt to file IP on optimized molecules to ensure that they have the freedom to develop the compound."

The Protein Data Bank archive is the single publicly accessible online repository of 3D structures for large biological molecules. The archive is maintained by members of the Research Collaboratory for Structural Bioinformatics consortium.

Partner perspectives

The Global Alliance for TB Drug Development and Medicines for Malaria Venture (MMV) see SDDC as a vehicle for augmenting their respective drug discovery pipelines.

"MMV has achieved a lot of success in the use of phenotypic screens to identify new antimalarial agents, but there is still an urgent need to identify new agents that can block transmission of the parasite, kill the dormant liver form of *Plasmodium vivax* and eventually eradicate malaria," said David Waterson, director of drug discovery at MMV. "The SDDC will aim to increase the number of validated biological targets and, by its use of structure-based design, provide MMV with an alternative strategy to strengthen its portfolio of discovery projects.

Such an approach will be particularly valuable when high throughput phenotypic screens are not available.”

“Projects undertaken by the SDDC will generate the crystal structures that will allow us to see how various molecules bind to their targets in *Mycobacterium*, which is going to be of paramount importance for doing structure-based drug design,” added Christopher Cooper, senior director of chemistry at the TB Alliance. “If you look for crystal structures of *Mycobacterium*-specific proteins, you will see that they are few compared with the number of crystal structures of proteins from other clinically relevant bacteria such as *Escherichia coli* and *Staphylococcus aureus*.“

Like MMV, Cooper said SDDC establishes a mechanism for feeding high-quality chemical series into the TB Alliance’s early stage drug development pipeline.

Cooper said that although the TB Alliance and SDDC still need to confirm the short list of a half-dozen or so essential, high-priority biochemical targets for drug discovery in TB, ATP synthase, RNA polymerase and DNA gyrase B of *M. tuberculosis* would likely be at the top of such a list.

Waterson said new biological targets identified from recent phenotypic screening efforts will form the basis of initial malaria-focused projects undertaken by SDDC. He said MMV has suggested a number of potential targets to the SDDC but declined to provide details.

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COMPANIES AND INSTITUTIONS MENTIONED

Bill & Melinda Gates Foundation, Seattle, Wash.

Center for Structural Genomics of Infectious Diseases, Evanston, Ill.

Global Alliance for TB Drug Development, New York, N.Y.

Medicines for Malaria Venture, Geneva, Switzerland

Midwest Center for Structural Genomics, Argonne, Ill.

National Institutes of Health, Bethesda, Md.

Seattle Structural Genomics Center for Infectious Disease, Seattle, Wash.

Structural Genomics Consortium, Toronto, Ontario, Canada

TB Structural Genomics Consortium, Los Angeles, Calif.