Albert Einstein College of Medicine Collaborates with GSK to Advance New Malaria Treatments

Like many researchers in academia, Professor Myles Akabas faced a challenge to gain access to a large chemical library. He and his team at Albert Einstein College of Medicine in Bronx, NY had developed an innovative approach to identify potential novel treatments for malaria, but they needed to partner with a pharmaceutical company with a large compound library to advance the research.

Malaria is a major health problem affecting large areas of the world and killing over half a million people per year, most of them women and children. It is caused by *Plasmodium* species parasites that grow inside red blood cells. One potential Achilles heel of the *Plasmodium* parasite is that in contrast to the human host, it cannot synthesize purines, organic molecules that are involved in many cellular processes and essential for parasite proliferation and survival. After infecting red blood cells, the *Plasmodium* parasite depends on its equilibrative nucleoside transporters (ENTs) to import purine precursors from its human host.

Prof. Akabas hypothesized that compounds that could bind and block the activity of parasite ENTs would kill the *Plasmodium* parasite by depriving it of its purine supply. His team designed a set of elegant screens to identify compounds with activity against ENTs. Testing a 65,000-compound library with collaborators at Columbia University demonstrated proof of principle for this approach and yielded some early hits. Promisingly, these were able to kill *Plasmodium* parasites in laboratory culture.

A timely opportunity

About this time, GSK launched the Discovery Fast Track Challenge. This program seeks innovative ideas for drug discovery that can be further enabled by high throughput screening (HTS) and therefore provided a mechanism by which the ENT inhibitor approach could be tested against a much larger chemical library. After being selected as a challenge finalist (from more than 140 applications) and visiting GSK to present his approach to a panel of GSK experts, Prof. Akabas was named as one of the first Discovery Fast Track winners.

Quickly afterwards, a joint team was formed between the Akabas lab and GSK scientists to adapt and run the screen against GSK's full HTS collection of nearly two million compounds.

"We had very complementary goals during the process," Prof. Akabas said. "Our project started out looking at the fundamental mechanics of purine transport into parasites and we realized this was a potentially good drug target. We developed and validated the assays to try and identity inhibitors – but that was as far as we could go without access to a much larger compound library. Collaborating with GSK has really provided that access."

Prof. Myles Akabas
Albert Einstein College of Medicine

Working and learning in partnership

The project was not without its challenges. The assays developed in the Akabas lab to screen ENTs used yeast cells, requiring the GSK team to engineer a room to accommodate the screens to avoid any risk of contaminating human cell cultures. Once this was established, GSK next adapted the assays to run in 1536-well plates, allowing the HTS run to be performed in around 10 days. Several hundred possible hits were found and run through additional assays to select the very best compounds, both within GSK's labs in Pennsylvania and with the Tres Cantos Open Lab Foundation facilities* in Spain and in the Akabas lab.

"The entire process has been a highly positive experience," said Prof. Akabas. "The GSK scientists have a tremendous amount of expertise in the HTS discovery process, both in the how to get it to work at the front end and then in analyzing the data. It was a more collaborative process than I had expected. They spent considerable time explaining the rationale for each step in the process from establishing the HTS in 1536-well format to the subsequent analysis and confirmation of the hits."

**http://www.openlabfoundation.org/about.html*

"I learned a tremendous amount about the issues that people in the high throughput screening field worry about that we knew nothing about. Different types of analysis of chemical structure, ligand efficiency and ways of looking at hits as to whether they are good starting points for drug development. Since I had no experience in drug development, this has been a great learning opportunity for me and my students".

On the path for future success

The best compounds from the Discovery Fast Track screen turned out to be around 10-fold more potent at inhibiting ENTs than anything previously known, killing *Plasmodium* parasites in culture. Several different chemical classes of inhibitors were also identified.

The results were obtained just as the National Institutes of Health (NIH) awarded Prof. Akabas and his Columbia University collaborators a five-year, $3.45 million grant (IR01AI11665) to develop anti-malarial drugs targeting ENTs.

One of the potential outcomes of the Discovery Fast Track challenge is to provide academic groups with confirmed hits that they can then further investigate and optimize. Given the importance of malaria and the fact that NIH funding had been granted to move the work forward, GSK and Prof. Akabas decided that this was the best option in this case. If Prof. Akabas and his team continue to make great progress, GSK may potentially partner again in the future via the Tres Cantos Open Lab Foundation program.

"The Discovery Fast Track Challenge provided us with a unique and productive opportunity to advance our project," Prof. Akabas said. "Not only did it give us the opportunity to screen a 1.8 million compound library with our assays, but more importantly, it gave us access to the expertise of GSK's scientists. This has provided us with both the knowledge and the tools to move our project to the next level, now with NIH support. Hopefully this will lead to the development of a new class of drugs to treat malaria."

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To learn more about GSK's Discovery Fast Track Challenge, please visit gsk.com/discoveryfasttrack