

Bringing into evidence

Researchers discuss partnerships in search of drugs to treat diseases that are of little interest to pharmaceutical companies

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Researchers from several countries met on November 13-14, 2014 at FAPESP headquarters to discuss potential cooperation in the development and delivery of new treatments for so-called neglected diseases, those that attract little interest from pharmaceutical companies because they affect mainly poor populations and countries. The list includes Chagas disease, visceral leishmaniasis, malaria and human African trypanosomiasis (sleeping sickness). The meeting was organized in conjunction with the Royal Society of Chemistry (RSC) of the United Kingdom and international organizations such as the Drugs for Neglected Diseases Initiative (DNDi) and the Medicines for Malaria Venture (MMV); it demonstrated that Brazil has much to offer, particularly in the areas of organic chemistry and molecular biology, in finding new drugs, even though articulation between research groups and

incentives for international collaboration in this area are rare in Brazil. “The event helped us understand how Brazil could be included in large studies of neglected diseases. We are interested in strengthening this relationship, because Brazil has a strong foundation in chemistry, and many diseases discussed at the meeting are endemic here,” says Alejandra Palermo, RSC’s open innovation manager.

According to data from the World Health Organization (WHO), neglected diseases affect about one billion people worldwide. Of the 17 diseases of this type listed by WHO, 14 are present in Brazil. Last year, RSC signed an agreement with two international organizations that are based in Switzerland, with the aim of developing new drugs. The Society has offered access to a network of collaboration in the field of organic chemistry and software to facilitate the exchange of information. According to Palermo, much work done by Brazilian research-

ers could continue to be conducted in consultation and in partnership with the two international organizations whose mission is to develop drugs that are affordable by poor populations.

An initiative underway involves the Synthetic Organic Chemistry Laboratory of the University of Campinas (Unicamp), with which the DNDi maintains an unprecedented program in Latin America entitled Lead Optimization Latin America (Lola). “The goal is to improve and conduct in vivo testing of chemical compounds to fight Chagas and Leishmaniasis,” says Luiz Carlos Dias, the laboratory coordinator at Unicamp. He says that working in a network, promoted by the international organization, enables the same molecule to be tested under different scenarios in various countries, thus accelerating the production process of a drug. In the last decade, the Society has been able to provide two new treatments for malaria, one



Children playing in a stream in Rondônia in the late afternoon, which is the optimum time for malaria-causing mosquitoes to bite

for sleeping sickness, and one for visceral leishmaniasis as well as a combination of drugs against visceral leishmaniasis specific to Asia and a pediatric treatment with a dose adapted for Chagas disease.

The task of analyzing and preparing a new Chagas compound has been divided among the Unicamp laboratory; the University of São Paulo's Center for Structural Molecular Biotechnology, coordinated by Professor Adriano Adricopulo; and the Physics Institute at São Carlos (São Paulo State). The project involves pharmaceutical companies, including AbbVie and Pfizer, and international research institutes including the Swiss Tropical Institute, in Switzerland, and the Drug Discovery Unit of the University of Dundee, in Australia.

In another pioneering initiative in Latin America, the Dias team is cooperating on MMV projects in Brazil Heterocycles, which is a program that has synthesized two promising molecules for the treatment of malaria. This project has collaborations with international centers, including the Imperial College London, Monash University of Australia, Glaxo Smith Kline in Spain, and Astra Zeneca and Syngene in India.

OBSTACLES

"The most expensive stages in the development of new drugs are the discovery of the molecule and preclinical and toxicity tests," says Glaucius Oliva, coordinator of the Center for Research and Innovation in Biodiversity and Drug Discovery (CIBFar), which is one of FAPESP's Research, Innovation and Dissemination Centers (RIDC), involved in one of the molecular synthesis projects coordinated by Carlos Dias's team at Unicamp. "With the financial support of large global organizations at precisely that stage, the pharmaceutical industry is then ready to begin clinical trials and large-scale production. That begins to pique the interest of the pharmaceutical industry in relation to neglected diseases," says Oliva, who was president of the National



“We need to form a large critical mass in the area of synthetic chemistry,” says Vanderlan Bolzani

1 The *Anopheles gambiae* mosquito, the vector for malaria

2 In the digitally treated images, the compound extracted from fluorescent flowers permeates two erythrocyte membranes, one infected with plasmodium malaria

able on the market. “Through in vitro tests we proved that betalains synthesized in the laboratory are able to overcome the malaria parasite membrane barrier. By using this technique, the usual dose of the drug can be reduced. Treatment efficiency improves because, by tracking the drug, we can find new ways to get the drug to the parasite,” Bastos says.

Research of this type could play an important role in the process of eradicating some diseases. “By improving what we already have, we can increase the efficacy of a treatment in the short term,” says Dr. Carolina Batista, the Latin America medical director of the DNDi. One example cited by her is the treatment of Chagas disease using benznidazole, the drug most frequently used to treat the disease, through a method created in the 1970s.

Between 2012 and 2013, the DNDi commissioned a large study comparing benznidazole with E1224, a new molecule that showed promise in the fight against Chagas disease. Although it had performed well in in-vitro tests, E1224 was inefficient in clinical trials with patients. One part of the study conducted with benznidazole, however, was shown to be effective in the treatment of patients chronically ill with the disease. Another study, published in 2014 by Spanish research institutions, found that benznidazole remains the most effective compound for treating Chagas. “Still, benznidazole has complicated side effects, such as allergic reactions and headaches. This shows that even an old and widely used drug still needs to be improved and researched,” says Dr. Batista.

Council for Scientific and Technological Development (CNPq). Oliva suggests that the partnership between the DNDi, MMV and Unicamp should serve as an example for other initiatives.

However, he notes other hurdles that Brazilian research must overcome to contribute more vigorously to studies of neglected diseases. One of these obstacles relates to pharmacokinetics, which concerns the mechanism by which a molecule travels in the body after administration. “Brazil still has very few people working in toxicology and synthetic and medicinal chemistry to create new molecules,” says Walter Colli, a biochemist and professor at the University of São Paulo (USP) and member of FAPESP’s Supervising Panel on Life Sciences.

A group of USP researchers has shown that the chemical synthesis of natural

compounds could improve the performance of existing drugs until new drugs are developed. The researchers were able to synthesize a molecule from betalains, which are pigments found in fluorescent flowers and beets. The compound has the ability to easily permeate animal cell membranes and serve as a fluorescent probe and marker for cell biology. “The fluorescent molecule can be functional, acting like a taxi, which only turns off its light when the drug is in the right place at the right time,” says Erick Bastos, a researcher with the Chemistry Institute at USP and the coordinator of the study.

The new molecule is in the testing phase. New drug development and pharmacological analyses are expensive, and Bastos’s group suggests that the compound could be used initially to improve the action of malaria drugs already avail-



One of the studies currently assessing the action of benznidazole involves the Dante Pazzanese Institute in São Paulo, WHO and institutions in Canada and Argentina. More than 3,000 patients were recruited from various countries, and the first results will be released in 2015. “We’ve already been able to analyze the effect of the drug on children with Chagas and have reached the conclusion that we can decrease the dosage of benznidazole in children,” says Sergio Sosa-Estani, a DNDi member and director of the National Institute of Diagnostics and Research on Chagas disease, based in Buenos Aires.

WIDENING THE SEARCH

Event participants emphasized, however, that new molecules to strengthen the fight against neglected diseases are needed. In 2012, the WHO released new guidelines for the control and elimination of these diseases by 2020. According to the organization, Chagas and leishmaniasis pose enormous challenges. In the case of Chagas disease, today approximately 7.6 million people are infected worldwide. However, when taking into account its risk factors, including inadequate housing in poorer regions, there are approximately 100 million people at risk of contracting the disease in Latin America alone, according to data from the DNDi. According to the WHO report, only 4.3% of total funding for research on neglected diseases is designated for Chagas and leishmaniasis research.

To correct this gap, the MMV and DNDi signed an agreement in London for the purpose of expanding research in this area. These institutions receive donations from governments,

companies and foundations such as the Bill & Melinda Gates Foundation. Jeremy Burrows, head of the MMV’s drug discovery department, explained that the organization’s goal is to develop new compounds to treat malaria, which each year affects 80 million to 100 million people worldwide. “We are now collaborating with more than 300 partners and with the help of Brazilian science we can make enormous contributions to the fight against malaria,” says Burrows.

The DNDi is the result of a partnership between public research institutions and the pharmaceutical industry. The organization was established with funds from the humanitarian organization, Doctors Without Borders, which won the Nobel Peace Prize in 1999 and today manages a network of 350 collaborative initiatives in 43 countries. “We

put universities and industry in contact; if they worked alone, they could not develop new products,” says Robert Don, the DNDi’s director of discovery and preclinical development.

For the British chemist, Simon Campbell, an RSC member and advisor for the two entities in collaborative projects with the Unicamp team, the Brazilian scientific community is known among those who conduct research on neglected diseases and has good laboratories and adequate levels of funding. However, he suggests that Brazil should invest more in the areas of synthetic and medicinal chemistry, to transform its knowledge base of biology into new treatments. “We need more effective treatments with fewer side effects. One way to speed up this process is to work in collaboration, and so we rely on the help of Brazilian scientists,” Campbell says.

This view is shared by Vanderlan Bolzani, a Chemistry Institute researcher at Universidade Estadual Paulista (UNESP). “We need to form a large critical mass in the area of synthetic chemistry, to encourage more young researchers to work with preparing molecules that can contribute to the eradication of diseases such as malaria and Chagas,” she says. Opening the meeting, FAPESP’s scientific director, Carlos Henrique de Brito Cruz, emphasized that the workshop is an opportunity to bring together researchers from São Paulo and elsewhere in the world as well as two important scientific foundations, FAPESP and the Royal Society of Chemistry. “The institutions involved are interested in sharing research information, so that results can be achieved more quickly,” says Brito Cruz. ■ Bruno de Piero

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