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REPRINT FROM JULY 30, 2015

STRATEGY

NEGLECTED ATTENTION

By Mark Zipkin, Staff Writer

Although the Drugs for Neglected Diseases initiative (DNDi) has made good on its 2003 promise to develop six therapies within 12 years, the not-for-profit wants to quicken the pace of progress for treatments that aren't likely to be advanced by the private sector alone. The organization is trying an experimental consortium designed to cut red tape and increase efficiency, in which it will forgo IP and provide compounds up front, while its corporate partners avoid disclosing their full range of molecules but provide relevant compounds from their own libraries, and operate in parallel rather than sequentially.

The DNDi deal, announced in May with AstraZeneca plc, Eisai Co. Ltd., Shionogi & Co. Ltd. and Takeda Pharmaceutical Co. Ltd., focuses on visceral leishmaniasis and Chagas disease. It was set in motion following the London Declaration, a 2012 World Health Organization (WHO) roadmap to accelerating work on neglected tropical diseases. The partnership has been labeled the Neglected Tropical Diseases Drug Discovery Booster consortium.

DNDi has had some successes with bilateral collaborations in the past, such as its 2004 partnership with Sanofi, which yielded ASAQ artesunate/amodiaquine for malaria. But Charles Mowbray, head of drug discovery at the organization, told BioCentury that operating multiparty collaborations has been consistently difficult because of the added bureaucracy and splintered resources.

"We had to keep the information siloed because of confidentiality," he said, adding that it took a lot of time and effort to manage all the partner relationships.

To create a more efficient system, Mowbray gathered the companies to find a new way of tackling projects collectively.

The system they devised begins with DNDi sharing "seed" compound structures with all four companies. The companies then search their own libraries *in silico* for similar compounds, which they send to Institut Pasteur Korea, an academic partner of the consortium, for *in vitro* screening against the target.

Top hits from the Pasteur screen are then shared with the four companies as the seed for the next round, and the partners search their libraries in parallel again for compounds close in structure to the top hits.

The model is a departure from the more common approach in which companies in a consortium only share their libraries with the organizing foundation.

In this case, the hits that originated in one company are shared with all four. In addition, the highly iterative nature of the project and the parallel activities of the partners are designed to speed up the process, in contrast to the standard model, which uses sequential screens performed by different partners.

The advantages of mining multiple libraries are clear, said Mowbray.

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>
> Charles Mowbray, DNDi

"Often there will be analogs of our precious hit residing in the collection of a company somewhere," he said. "If they go look in their collections, and then pick out using their best computational methods the hundred most similar compounds and send those to us, we could test them. With four or more companies at once, we could perhaps develop a structure-activity relationship — a process that would normally take us months or years — in just a few months."

EXPERIMENTAL MODEL

According to Michael Gottlieb, associate director of science at the Foundation for the National Institutes of Health (FNIH), speeding up drug development is particularly needed in neglected diseases.

"The drugs for these diseases are terrible, to say the least," he told BioCentury. "Given the population and the market, there's not a lot of interest in industry in doing R&D around new drugs for trypanosomatids."

In the last six years, at least five public-private partnerships have been formed to develop drugs for neglected tropical diseases, exlcuding malaria. (See "Pooling Resources for Neglected Tropical Diseases")

Recent attempts to shorten the process have focused on repurposing approved drugs for this space. In 2011, the National Institutes of Health launched the NIH Chemical Genomics Center Pharmaceutical Collection to make approved drugs and bioactives publicly available through the Therapeutics for Rare and Neglected Diseases (TRND) program run by the National Center for Advancing Translational Sciences (NCATS).

DNDi's new approach is unique, said Gottlieb. "There are other mechanisms by which companies will share libraries with another group. What I think is novel is whatever characterization of the hit they've gotten, for that to become the feed for the next round," and for those seeds then to be spread to the different companies.

"Nobody's done this before, not like this," Mowbray told BioCentury. "First and foremost, this is an experiment for DNDi for two neglected tropical diseases. If it works there, it could be expanded to some other neglected diseases. Certainly our colleagues working at some of the other product development partnerships on malaria and TB are looking with interest and waiting to hear how we get on with this."

One of the big advantages, according to Mowbray, is how they're handling IP, which is always a major sticking point in multilateral collaborations. In this system, DNDi isn't looking to hold any of the IP.

"There isn't a commercial return here," says Mowbray. "We're not interested in commercial applications, but if we can find an interesting hit and interesting analogs, and then do the development of that towards treating patients for Chagas disease or leishmaniasis, they'll grant us the license."

He added that compounds originating at a company may be included in existing or future patent applications by the company.

SOWING THE SEED

The project has begun with DNDi providing all four companies with several seed compounds generated from its earlier programs or from published sources that previously showed promise against *Leishmania donovani*, the cause of visceral leishmaniasis, or *Trypanosoma cruzi*, the cause of Chagas disease.

The project is now in its third iterative round from the first candidate compound, and the partners may also perform a fourth.

Mowbray believes the strengths of the new approach can be assessed long before a drug makes it to approval.

He said the first milestone will be for DNDi to show efficacy for improved analogs of its first seed in preclinical models of leishmaniasis and Chagas disease, which is expected in early

POOLING RESOURCES FOR NEGLECTED TROPICAL DISEASES

Selected public-private partnerships formed since 2009 that aim to perform research and develop drugs for neglected tropical diseases. Does not include malaria, or partnerships formed solely to advance a company's compounds. *Source: BCIQ: BioCentury Online Intelligence; BioCentury Archives; DNDi; Schistosoma Epigenetics - Targets, Regulations, New Drugs (SEtTReND) website*

DATE	TITLE	COMPANIES	INSTITUTIONS	DISEASES	DISCLOSED FUNDING
May 2015	Neglected Tropical Diseases Drug Discovery Booster	**AstraZeneca plc** (LSE:AZN; NYSE:AZN); **Eisai Co. Ltd.** (Tokyo:4523); **Shionogi & Co. Ltd.** (Tokyo:4507); **Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502)	**Drugs for Neglected Diseases initiative** (DNDi); **Institut Pasteur Korea**	Leishmaniasis, Chagas disease and African trypanosomiasis	€640,000 ($710,000) from **Global Health Innovative Technology (GHIT) Fund**, undisclosed remainder from DNDi
April 2014	PDE4NDP (PhosphoDiEsterase inhibitors for Neglected Parasitic Diseases) project	**Iota Pharmaceuticals Ltd.**	**European Commission**; **European ScreeningPort GmbH**; **Oswaldo Cruz Foundation**; **Spanish National Research Council** (CSIC); **Theodor Bilharz Research Institute**; **Top Institute Pharma**; **University of Antwerp**; **University of Glasgow; University of Kent**; **VU University Amsterdam**	Leishmaniasis, Chagas disease, African trypanosomiasis and schistosomiasis	Project received €7.6 million ($8.4 million) under the EU's Seventh Framework Programme and from partners' contributions

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January 2013	SEtTReND	iNovacia AB subsidiary of **Kancera AB** (SSE:KAN)	**Federal University of Rio de Janeiro**; **Institute of Genetics and Molecular and Cellular Biology** (IGBMC); **Institut National de la Santé et de la Recherche Médicale** (INSERM); **Pasteur Institute of Lille**; **Martin Luther University Halle-Wittenberg**; Oswaldo Cruz Foundation; **University of California San Francisco**; **University of Freiburg**; **University of São Paulo**	Schistosomiasis	€3.3 million ($3.7 million) from the European Commission
May 2011		**Sanofi** (Euronext:SAN; NYSE:SNY)	DNDi;	Leishmaniasis, Chagas disease, African trypanosomiasis, lymphatic filariasis, onchocerciasis, soil-transmitted helminthiasis, dracunculiasis, fascioliasis and schistosomiasis	Not disclosed
November 2009		**Pfizer Inc.** (NYSE:PFE)	DNDi; **Griffith University**; Institut Pasteur Korea	Visceral leishmaniasis, Chagas disease and African trypanosomiasis	Not disclosed

2016. The compounds will be cultured in macrophages *in vitro* and tested for their ability to selectively kill the *L. donovani* and *T. cruzi* parasites.

In early 2017, DNDi expects to have completed the iterative screening rounds for four initial seeds for each indication. "We aim that, as a result, at least one new chemical series for each disease will be ready for *in vivo* proof-of-concept experiments, or for focused medicinal chemistry to optimize a series," said Mowbray.

At the conclusion of the Drug Discovery Booster process, Mowbray said, the best-case outcome is to move exceptionally promising lead compounds and their analogs to the next phase of development, in which other typical drug properties like ADME, PK, safety and solubility can be evaluated.

Regardless, he said, the ability to evaluate multiple lead compounds simultaneously during the iterative rounds is an inherent advantage over more traditional hit-to-lead chemistry approaches.

Core institutional funds, raised from both public and private donors, support AstraZeneca's contributions to the consortium, and the Japanese Global Health Innovative Technology (GHIT) Fund is supporting the three Japanese pharmas.

Separately, on July 27 DNDi and Takeda announced an agreement in which DNDi will perform lead optimization on the pharma's compounds from a new aminopyrazole series for visceral leishmaniasis. The project is supported by a $4 million investment from GHIT.

COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland
Eisai Co. Ltd. (Tokyo:4523), Tokyo, Japan
Foundation for the National Institutes of Health (FNIH), Bethesda, Md.
Global Health Innovative Technology (GHIT) Fund, Tokyo, Japan
Institut Pasteur Korea, Seongnam, South Korea
National Center for Advancing Translational Sciences (NCATS), Bethesda, Md.
National Institutes of Health (NIH), Bethesda, Md.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Shionogi & Co. Ltd. (Tokyo:4507), Osaka, Japan
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
World Health Organization (WHO), Geneva, Switzerland

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