RESEARCH

Screening

OBJECTIVE: Use high throughput screening to identify novel hit series for leishmaniasis from synthetic compound collections accessed from partners or acquired from commercial suppliers, and expand screening activities to natural products that are a promising source of novel active series

More than 20 novel series were identified in 2017 and are now being progressed.

Leish H2L

OBJECTIVE: Identify new lead series from current ongoing hit-to-lead activities by taking advantage of the optimization consortia and screening platforms for leishmaniasis

The process of hit-to-lead optimization is ongoing with multiple series from several pharmaceutical companies and with hits from libraries purchased from commercial vendors and screened by DND*i* to be advanced if promising activity can be shown in pre-clinical models.

Booster H2L

NEW!

OBJECTIVE: Speed up the process and cut the cost of finding new treatments for leishmaniasis by bringing together pharmaceutical companies in a multilateral, simultaneous, and non-competitive search process

The Drug Discovery Booster was launched in 2015 to circumvent early-stage commercial barriers between pharmaceutical participants, allowing DND*i* to search millions of unique compounds simultaneously in the hunt for new treatment leads.

In 2017, two new companies - AbbVie and Merck - signed on to the Drug Discovery Booster, joining Takeda, Eisai, Shionogi, AstraZeneca, and Celgene.

To date, 32 iterations of the booster have been launched around 16 distinct seed compounds. Ten hit series have been identified, four of which will enter into proof-of-concept *in vivo* efficacy studies by Q1 2018.

Daiichi-Sankyo LH2L
(leishmaniasis hit-to-lead)

NEW!

OBJECTIVE: Identify at least one – possibly two – progressable lead series meeting DND*i* lead stage criteria for visceral leishmaniasis

Current hit-to-lead efforts of the series identified from the Daiichi Sankyo Pharma Space Library focus on Chagas disease (see p. 52), but the project team submits any newly synthesized molecules to a *Leishmania* cross screen to assess potential.

Towards new-generation treatments for leishmaniasis

DND*i*'s recent efforts to develop modern treatments for leishmaniasis through its discovery pipeline are bearing fruit. DND*i* and partners (GSK, DDU and Wellcome Trust at University of Dundee, Novartis, Pfizer, Takeda, and Celgene) have built an unprecedented portfolio of ten new chemical classes (four lead series, four pre-clinical candidates, and two clinical candidates) with different mechanisms of action against *Leishmania* parasites.

RESEARCH

DNDI-5421 & DNDI-5610

OBJECTIVE: Maintain back-up candidate oxaboroles that could replace the drug candidate DNDI-6148, if needed

These two compounds from the oxaborole class serve as back-ups to DNDI-6148. Their further development is currently on hold and will only recommence should problems be encountered with the development of DNDI-6148.

Aminopyrazoles

OBJECTIVE: Select a pre-clinical candidate from the aminopyrazole series for the treatment of leishmaniasis

DNDI-5561 was nominated as a new pre-clinical candidate from the aminopyrazole series in October 2017. Four back-up compounds are well advanced and offer similar profiles to DNDI-5561. Additional studies, including preliminary toxicology assessments, are being planned to further understand the safety profiles of these compounds and to identify the best back-up to DNDI-5561. DND*i* developed this aminopyrazole series from a high-throughput screening hit from a Pfizer compound library.

RESEARCH

CGH VL series 1

OBJECTIVE: Select a pre-clinical candidate from the Celgene Global Health VL series for the treatment of VL

DND*i*'s collaboration with Celgene Global Health continues to explore the potential of this series to deliver a pre-clinical candidate. Compounds with much improved physical properties, including improved aqueous solubility, were identified in 2017.

Leish L205 series

NEW!

OBJECTIVE: Progress a compound from the 205 series towards candidate selection and nomination for further pre-clinical development for VL

Following proof-of-principle with the 205 series for VL, compounds from this series have shown a 100% parasite load reduction in liver and spleen in a VL murine model. Further characterization of this series is ongoing. Over 400 compounds have been synthesized to date in this lead optimization programme for Chagas disease and leishmaniasis.

TRANSLATION

DNDI-0690 nitroimidazole

OBJECTIVE: Progress DNDI-0690, a nitroimidazole compound, through clinical development for the treatment of leishmaniasis

DNDI-0690, a nitroimidazooxazine for the treatment of VL and possibly CL, was selected for pre-clinical development in September 2015. A full pre-clinical toxicology and safety studies package was completed in 2017, and the decision to progress to a Phase I single ascending dose study in healthy volunteers is anticipated in early 2018.

TRANSLATION

DNDI-6148

OBJECTIVE: Progress DNDI-6148, an oxaborole compound, through clinical development for the treatment of leishmaniasis

DND*i* and Anacor have been working together over the last few years to identify oxaborole compounds, initially for the HAT programme, but this work has now expanded to include both leishmaniasis and Chagas disease. DNDI-6148 has emerged as a promising lead candidate for VL and CL, and by the end of 2015, studies including exploratory toxicology necessary for possible progression to pre-clinical development had been successfully completed. In January 2016, DNDI-6148 was nominated as a pre-clinical candidate for the treatment of VL and possibly CL.

The pre-clinical toxicology package was completed in 2017, and the decision was made to progress to Phase I single ascending dose in healthy volunteers in parallel with additional toxicological investigations.

DNDI-5561

NEW!

OBJECTIVE: Progress DNDI-5561, a selected aminopyrazole compound, to Phase I clinical studies for the treatment of VL

This project is the continuation of the optimization of the aminopyrazole series for VL. With the funding of the Japanese GHIT Fund, DND*i* and partner Takeda worked with the objective of delivering an anti-parasitic aminopyrazole drug, as well as back-up candidates. DNDI-5561 is the front-running second-generation aminopyrazole.

Following positive results from efficacy and safety studies, DNDI-5561 was selected as a pre-clinical candidate in October 2017.

GSK3186899 / DDD853651 & GSK3494245 / DDD1305143

NEW!

OBJECTIVE: Progress pre-clinical development of compounds for leishmaniasis

In April 2017, DND*i* and GSK entered into an agreement for the pre-clinical development of two compounds for leishmaniasis which were discovered by GSK in collaboration with the Drug Discovery Unit (DDU) at the University of Dundee, following some co-funding by the Wellcome Trust.