Headlines Promising Results from the VL Lead Optimisation Consortium with Advinus

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Description

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Lead optimisation (LO) involves taking a "lead", or a molecule known to kill a specific parasite in both *in vivo* and*in vitro* assays, and optimising it by making chemical modifications that will optimise the molecule"s capacity to be absorbed into the bloodstream, be distributed effectively to the infection sites, survive in the body, and kill the parasite, and not be harmful when it reaches the patient. Researchers aim to satisfy all these ADME/T (Absorption, Distribution, Metabolism and Excretion/ Toxicology) parameters in order for the molecule to be progressed as a drug candidate(1).

Since its inception in November 2007, the VL-specific LO consortium has made significant headway in identifying compounds that effectively kill the *Leishmania* parasite and that hold the potential for "druggability". A dedicated research team of 12 individuals based at the two main partner sites- Advinus Therapeutics (responsible for medicinal chemistry, ADME/T) and the Central Drug Research Institute (responsible for conducting the *in vitro*and *in vivo* screening) - has closely collaborated to optimise the promising lead series of 2-quinolines.

A budding series- the 2 -substituted quinolines Alain Fournet and collaborators at the Institut de Recherche pour le Developpement (IRD) originally isolated the 2-quinolines from Bolivian plants which are used in traditional medicine to treat cutaneous leishmaniasis and malaria. After some promising early results, the DND*i*-managed LO consortium has synthesised over 220 diverse analogues of 2-quinolines. These modified quinolines were significantly more effective than the parent compounds and a few compounds have shown >90% parasite killing at <1.0 IM. Metabolic stability, which is a known liability of this series, has been improved through the introduction of halogen substituents in more than ten compounds. Further studies of the most promising compounds will be done to confirm the druggability and *in vivo* efficacy and safety.

Partnership in action: Shing Chang, Denis Martin, and Bhawna Sharma of DND*i* visiting members of the lead optimisation team at Advinus in 2008

Hedging bets with other classes of interest

While this series holds great promise, DND*i* and partners are aware of the highly attritive process of drug development - simply put, these compounds could still easily fail as development progresses. In order to ensure that one new drug candidate is in clinical development by 2013, DND*i* is also looking at a number of other potentially interesting compounds, including buparvaquone, the class of oxaboroles, and new formulations of amphotericin B. This strategy and the promising early results were presented during the WorldLeish4 meeting and are available at www.dndi.org.

"WorldLeish4" was a great opportunity for us to interface with the "leishmaniacs" and to share some of the exciting results we have generated so far in this field and to discuss plans related to our collaboration within DNDi"s VL-specific LO programme. Both Vadiraj, Gopinath, Assistant Director at Advinus, and I welcome such future interactions and look forward to sharing news of promising drug candidates at the next WorldLeish in Brazil."

Dr. Kasim Mookhtiar, Chief Scientific Officer at Advinus Therapeutics, India