Fact Sheet on GSK-TB Alliance Partnership
March 2005

TB Drug Discovery Projects Use New Modes of Action

The joint research program currently consists of a portfolio of four projects designed to yield new compounds that attack *Mycobacterium tuberculosis (M. tb)* on multiple levels. Drug candidates arising from these projects could shorten the treatment time for patients with TB and, because of their novel mechanisms of action, treat patients who are resistant to conventional therapies.

The compounds will also be screened for their ability to be taken simultaneously with antiretrovirals (ARVs), which are used to treat HIV/AIDS patients. One-third of the 39 million people infected with HIV worldwide are co-infected with TB, and TB is a leading cause of death among people infected with HIV/AIDS. Although joint TB-HIV treatment is a public health priority, simultaneous TB-HIV treatment is extremely difficult because of drug-drug interactions between some ARVs and existing TB drugs.

The most advanced drug discovery project, which is at the lead optimization stage, is exploring a novel class of antibiotics, the pleuromutilins, for a TB indication. Pleuromutilins inhibit bacterial protein synthesis, and compounds in the class have already been shown to inhibit the growth of *M. tb in vitro*. Derived from natural products and possessing a unique mechanism of action, the pleuromutilins do not have cross-resistance with other antibiotics and produce resistance very slowly.

Two of the remaining three projects are designed to attack novel mycobacterial targets. By inhibiting enzymes critical to the functioning of *M. tb,* these approaches may disable the bacterium without harming the human host and are being developed to significantly shorten the duration of treatment. These projects have already progressed to the lead identification stage and target the isocitrate lyase (Icl) and InhA enzymes. Icl is required to provide nutrients essential for *M. tb* to survive under conditions of slow growth. Drug candidates emerging from this program are expected to be effective at killing persistent or slow-growing bacteria. The other lead identification project is based on InhA, an enoyl-ACP reductase enzyme involved in the synthesis of fatty acids in *M tb*. Inhibitors of this enzyme have the capacity for excellent bactericidal activity without causing the resistance often associated with isoniazid, a cornerstone anti-TB drug.

Finally, GSK will screen its antimicrobial libraries for novel compounds that have the ability to kill *M. tb.* The testing will select compounds that are active against specific molecular targets; these compounds include inhibitors of DNA gyrase, peptide deformylase and analogs of quinolone electron transport inhibitors.

The collaboration will be overseen by a Joint Steering Committee, with representatives from both parties, which will establish criteria for the projects and meet regularly to monitor progress. The TB Alliance will help support 25 full-time scientists dedicated exclusively to the TB drug program. GSK will cover overhead costs for the associated projects at its Tres Cantos facility, dedicated to the diseases of the developing world. GSK will also contribute a matching number of staff as well its drug discovery expertise.

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