Working Group TB Drug R&D Portfolio 2008

Discovery – high throughput screening (target based or whole cell) or rational design		
Actinomycete metabolite screening Univ. Illinois Chicago	**Energy Metabolism Inhibitors** TB Alliance, Univ. Illinois Chicago, Univ. Pennsylvania	**Fungal metabolite screening** Univ. Illinois Chicago
GSK Focused Screening TB Alliance, GlaxoSmithKline	**Malate Synthase Inhibitors** TB Alliance, GlaxoSmithKline, Texas A&M University	**Persistence Target Discovery (target-based screening)** Vertex Pharmaceuticals
Phenotypic Screening TB Alliance, Univ. Illinois Chicago	**Protease Inhibitors** TB Alliance, Infectious Disease Research Institute	**Screen for Synthetic Lethality in *M. tuberculosis*** Johns Hopkins University
Target discovery (phenotypic screening) Vertex Pharmaceuticals	**TAACF ChemBridge Library Screening** NIAID, NIH; Southern Research Institute	**RNA Polymerase Switch Region** Rutgers University; Howard Hughes Medical Institute; NIAID, NIH
Discovery – hit to lead (defined on reverse)		
InhA inhibitors TB Alliance, GlaxoSmithKline	**Summit plc. Compounds** The Lilly TB Drug Discovery Initiative	**Tuberculosis Protein Kinase Inhibitors** Vertex Pharmaceuticals
Discovery – lead optimization		
Dipiperidines Sequella, Inc.	**Homopiperazines and Piperazines** Sequella, Inc.	**Multifunctional Molecules** TB Alliance, University of Auckland, Colorado State University
Mycobacterial Gyrase Inhibitors TB Alliance, GlaxoSmithKline	**Pleuromutulins** TB Alliance, GlaxoSmithKline	**Riminophenazines** TB Alliance, IMM, BTTTRI, Univ. Illinois Chicago
TL1 Inhibitors Sequella, Inc.		
Preclinical – candidate selected, animal efficacy studies		
CPZEN-45 The Lilly TB Drug Discovery Initiative	**DC-159a - Quinolone** Research Institute of Tuberculosis, JATA	**Nanodrug delivery system for anti-TB drugs** CSIR, South Africa
Nitroimidazoles TB Alliance, University of Auckland, Univ Illinois Chicago	**SQ73 -Ethylenediamine** Sequella, Inc.	**SQ609 - Dipiperidine** Sequella, Inc
SQ641 - Nucleoside-based capuramycins (Translocase inhibitor) - Sequella, Inc.		
Advanced preclinical – GLP pharmacology/toxicology in animals for regulatory submission, specifically including repeat dosing GLP toxicology		
TB Oxazolidinone PNU-100480 Pfizer	**TBK-613 - Quinolone** TB Alliance, various CROs	
Clinical Phase I		
Diamine SQ-109 Sequella Inc.	**Linezolid – *Ph1/2* (TBTC Study 30)** CDC TBTC, Pfizer, various Universities*	**Pyrrole LL-3858 (Sudoterb) – *PhI completed; PhIIa protocol submitted***. Lupin Pharmaceutical Inc
Clinical Phase II		
Diarylquinoline TMC207 Tibotec	**Nitro-dihydro-imidazooxazole OPC-67683** Otsuka Pharmaceutical Co.	**Nitroimidazole-oxazine PA-824** TB Alliance
Rifapentine (TBTC Study 29) CDC TBTC, sanofi-aventis		
Clinical Phase III		
Gatifloxacin – OFLOTUB Consortium, European Commission, Lupin, WHO TDR	**Latent TB Infection TBTC Study 26** CDC TBTC, Department of Veterans Affairs	**Moxifloxacin** TB Alliance, Bayer, CDC TBTC, Johns Hopkins Univ, BMRC, UCL

Reflects information on specific projects submitted to the WGND by October 13, 2008. To update or add projects, please contact StopTBDrugWG@tballiance.org

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What is the Stop TB Partnership Working Group on New Drugs?
One of the Stop TB Partnership's seven Working Groups, the Working Group on New Drugs (WGND) is a network of expert individuals committed to accelerating the development of effective and affordable new therapies for TB. The WGND acts as a forum to facilitate global collaborations for the development of new TB drugs and promotes coordination of all stakeholders in this process. For further information, or to join the Group, please visit the WGND website at: http://www.stoptb.org/wg/new_drugs/.

About this Portfolio: Purpose and Criteria for Inclusion
A robust and sustained pipeline of TB drug candidates and discovery programs is essential to successful development of new TB drug regimens. TB must be treated with a combination of drugs, thus prospective new drugs must be evaluated for compatibility and complementarity. With the aim of increasing efficiency and coordination of the global TB drug R&D enterprise through information-exchange, the WGND conducts an annual survey of the TB drug R&D activities of WGND members. This exercise also identifies critical gaps in resources and capacity.

For the purpose of this particular survey, WGND members were asked to submit information on clinical and preclinical development programs in progress as well as ongoing drug discovery projects (at the high throughput screening, hit to lead or lead optimization stage), including projects that address new indications for existing drugs or chemical optimization/ reformulation of currently available drugs. The chart overleaf lists the projects brought to the Group's attention that meet these criteria and provide specific information about the activity, e.g. a compound, target, trial or screen name.

Portfolio Updates and Publication of Full Survey Results
The portfolio chart overleaf will be updated as needed, and, at least at quarterly intervals, in response to additions and changes submitted by WGND members. To add or update information please go to http://www.tballiance.org/working-group/activity-form-new.php

Updated versions will be available at: http://www.stoptb.org/wg/new_drugs/projects.asp.

In addition, detailed information submitted on each project will be published as a compendium, via the same website, by December 31 2008

Additional Surveys Planned for 2009 – Watch this Space!
This portfolio reflects only a portion of Global TB drug R&D activities and only a fraction of WGND member activities impacting TB drug R&D. In 2009, the WGND will attempt additional surveys to catalog (1) Global TB drugs R&D activities and (2) WGND member capabilities and projects.

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DEFINITIONS:
Hit: A compound with a defined chemical structure that gives a positive readout in a *M. tuberculosis* target or whole-cell based assay and has been confirmed by resupplied material
Lead: A compound with acceptable physiochemical properties that has demonstrated activity against *M. tuberculosis*, selectivity against the pathogen and tractable structure-activity relationships

ABBREVIATIONS:
BMRC: British Medical Research Council; BTTTRI: Beijing Tuberculosis and Thoracic Tumor Research Institute; CDC TBTC: Centers for Disease Control TB Trials Consortium; CSIR: Council for Scientific and Industrial Research, South Africa; IMM: Insitute of Materia Medica; JATA: Japan Anti-Tuberculosis Association; NIAID, NIH: National Institute of Allergy and Infectious Diseases, National Institutes of Health; TAACF: Tuberculosis Antimicrobial Acquisition and Coordination Facility; WHO TDR: WHO Special Programme for Research and Training in Tropical Diseases; UCL: University College London.

*For Linezolid Clinical Phase I study, various University partners are Univ. KwaZulu, Columbia University, Yale Univ., Univ. Texas, Univ. Cape Town, Univ. Boston