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Excellent prospects for a new drug to fight the Tuberculosis pandemic and combat XDR-TB

Summary
The New Medicines for Tuberculosis (NM4TB) consortium is pleased to announce the discovery of a new drug candidate, the benzothiazinones, (BTZ), with excellent prospects for fighting not only Tuberculosis (TB), but also for combating the Extensively Drug Resistant (XDR-TB) form of the disease.

Tuberculosis
TB is one of the oldest infectious diseases known to man and its agent, *Mycobacterium tuberculosis*, has infected one third of the world's population. As a result, someone dies from the disease every 15 seconds and 30 million more people will lose their lives to TB in the next decade. Although directly observed short course chemotherapy (DOTS) is available to treat the disease, this treatment is old, slow and inefficient by the current standards of the pharmaceutical industry. Furthermore, multidrug resistant strains have appeared in increasing numbers during the past 15 years as the global TB and HIV epidemics have intersected as poverty spreads. Now, with increased public and private funding, some of the most innovative approaches are being used to identify and validate targets for new TB drugs, and to implement the screening and medicinal chemistry processes required to identify lead compounds for the generation of candidate drugs.

BTZ
Prof Stewart Cole, Dr Vadim Makarov, Dr Ute Möllmann, Prof Giovanna Riccardi, and their colleagues have identified a novel class of compounds called benzothiazinones (BTZ) that act by preventing the TB bacterium from constructing its cell wall. In particular, one member of the class, BTZ043 was extremely potent, killing the TB agent, both in test tube experiments and in mouse models of the disease. BTZ043 is as effective as the two main drugs (Isoniazid and Rifampicin) in reducing the bacterial levels in the lungs and spleens of infected mice. The target of the new class of compounds is a component of Mycobacterium's cell-wall-building machinery that has never before been used as a drug target. The most advanced compound of this new class, BTZ043, is a candidate for inclusion in combination therapies for both drug-sensitive and extensively drug-resistant TB.

XDR-TB
Extensively Drug Resistant TB *(*XDR-TB) is a new threat that came to the world's attention in August 2006 when an epidemic of extremely virulent TB was reported in Natal, South Africa. Within 25 days of diagnosis, no less than 52 of the 53 patients died, and XDR-TB has now caused 300 deaths in South Africa. Every country is at risk as the World Health Organisation (WHO) has identified XDR-TB in all regions of the world. Drug resistance is likely to continue to spread as long as the current, six-month long TB treatment programme remains the front-line attack against TB. Faster acting drugs are

required and BTZ offers a potential alternative to current treatments.

NM4TB

New Medicines for Tuberculosis (NM4TB) is a research consortium funded by the European Commission (EC), which aims to develop new drugs for successful and shorter treatment of TB through a fully integrated approach. The consortium includes 34 research groups from 14 different countries (Switzerland, France, United Kingdom, Italy, Slovakia, Sweden, Germany, Hungary, Denmark, Korea, the USA, the Russian Federation, South Africa and India). NM4TB runs an ambitious drug discovery project that combines some of Europe's leading academic TB researchers with a major pharmaceutical company (Astra-Zeneca) and three SMEs, all with a strong commitment to discovering new anti-infective agents. NM4TB has a comprehensive portfolio of potential and validated targets plus several novel, proprietary anti-TB agents in its drug development pipeline (http://www.NM4TB.org).

The NM4TB consortium is led by Prof. Stewart T. Cole FRS, the Director of the Global Health Institute at Switzerland's Federal Institute for Technology (EPFL) at Lausanne.

Quotes

Professor Stewart Cole, the Scientific coordinator of NM4TB stated *"We are very excited by the prospects offered to TB treatment by BTZ and thanks to the identification of its target are already able to develop back-up compounds."*

Professor Jacques Grosset MD of the Center for TB Research, Johns Hopkins University School of Medicine: "*BTZ is a promising new lead in drug discovery for TB. We should now measure its exact potential for the cure of TB and especially of MDR and XDR TB, and for that we must persevere in our collaborative efforts.*"

Professor Giovanna Riccardi of the University of Pavia: "*In the past, Isoniazid, the main antitubercular drug, was defined as a "magic bullet" to fight tuberculosis; with the results achieved by NM4TB Consortium we can affirm that we have found the "magic target*"."

Dr Tanjore Balganesh, Head of Research, AstraZeneca India (Bangalore): "*AstraZeneca is proud that the skills and experience of our infection research scientists have contributed to this exciting discovery of a new class of compound with potential to treat the ongoing challenge that is TB."*

Professor Philip Butcher, St George's University of London: "*To identify a potentially new drug to treat TB is a great achievement, made possible through EU funding to the NM4TB consortium. This is a good funding model for future drug discovery programmes for global diseases of poverty, such as TB, which are often neglected by commercial R&D programmes. Subsequent*

clinical trials of this new drug in people with TB must be fully funded to finally realize the potential of our scientific effort."

Notes

NM4TB can be contacted by phone at +41 21 6931851 or by e-mail at stewart.cole@epfl.ch. NM4TB's website is located at http://www.NM4TB.org

Sites

Sites participating in the New Medicines for Tuberculosis (NM4TB) benzothiazinone drug development programme:

École Polytechnique Fédérale de Lausanne (EPFL - Swiss Federal Institute of Technology), Switzerland
Prof. Stewart T. Cole FRS, EPFL SV GHI UPCOL AI 2151 (Bâtiment AI) Station 15 CH-1015 Lausanne Switzerland Tel: +41 21 6931851 Secretary: +41 21 693 1787 Fax: +41 21 693 1790 E.mail: stewart.cole@epfl.ch Web: http://ghi.epfl.ch

AstraZeneca R & D, Bangalore, India
Dr. Tanjore Balganesh, Bellary Road Hebbal Bangalore India Tel: + 91 80 23622001 Tel 2: + 91 80 23621212 Fax: + 91 80 23622002 E.mail : tanjore.balganesh@astrazeneca.com Web: http://www.astrazenecaindia.com/

Institut Pasteur, France
Integrated Mycobacterial Pathogenomics Unit
Dr Roland Brosch, Integrated Mycobacterial Pathogenomics Institut Pasteur 25-28, rue du Docteur Roux 75724 Paris Cedex 15 France Tel: + 33 1 45 68 84 46 Fax: + 33 1 40 61 35 83 E.mail: rbrosch@pasteur.fr Web: http://www.pasteur.fr/recherche/unites/Pmi/

Università degli Studi di Pavia, Italy
Prof. Giovanna Riccardi, Dipartimento di Genetica e Microbiologia Laboratorio di Microbiologia Molecolare Università degli Studi di Pavia, via Ferrata, 1 27100 Pavia Italy Tel: + 39 0382 985574 Fax: + 39 0382 528496 E.mail: riccardi@ipvgen.inpv.it Web: http://www.unipv.it/eng/home_eng.html

Statens Serum Institut, Denmark
Dr. Ida Rosenkrands, Statens Serum Institut Department of Infectious Disease Immunology Artillerivej 5 DK-2300 Copenhagen S Denmark Tel: + 45 32 68 37 21 Fax: + 45 32 68 30 35 E.mail: idr@ssi.dk Web: http://www.ssi.dk

Leibniz-Institut für Naturstoff-Forschung und Infektionsbiologie - Hans-Knöll-Institut, Germany
Dr. Ute Möllmann, Department of Molecular and Applied Microbiology Leibniz Institute for Natural Product Research and Infection Biology - Hans Knoell Institute Beutenbergstr. 11 D-07745 Jena Germany Tel: +49 (03641) 532 10 98 Fax: +49 (03641) 532 08 12 E.mail: ute.moellmann@hki-jena.de Web: http://www.hki-jena.de

Comenius University, Faculty of Natural Sciences, Slovakia

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Dr. Katarina Mikusova, Department of Biochemistry Comenius University, Mlynska dolina 84215 Bratislava Slovakia Tel: + 421 2 60296 547 Tel2: + 421 2 60296 452 Fax: + 421 2 60296 452 E mail : mikusova@fns.uniba.sk Web: http://www.fns.uniba.sk

St. George's University of London, United Kingdom
Prof. Philip Butcher, Dept. Cellular & Molecular Medicine, St. George's University of London Cranmer Terrace London SW17 ORE United Kingdom Tel: + 44 208 725 5721 Fax: + 44 208 672 0234 E.mail : butcherp@sgul.ac.uk Web: http://bugs.sgul.ac.uk

A. N. Bakh Institute of Biochemistry of the Russian Academy of Science
Dr. Vadim Makarov, A. N. Bakh Institute of Biochemistry of the Russian Academy of Science, 119071 Lenensky prospect 33, Moscow, Russian Federation. Phone: + 7 916 6408316 (mobile) or + 7 495 3831251 (home). E.mail: makar-cl@ropnet.ru

Institut Pasteur Korea
Dr. Priscille Brodin, Inserm Avenir Group, Institut Pasteur, Korea, 39-1, Hawolgok-dong, Seongbuk-gu, Seoul, 136-791, Korea. Tel: +82 2 3299 0321. Fax: +82 2 3299 0210. E.mail: pbrodin@ip-korea.org Web: http://www.pasteur.or.kr/group/index.jsp?g_seq=1&c_seq=1

Johns Hopkins University School of Medicine
Prof. Jacques Grosset, MD, Center for TB Research, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA. Tel: 410-955-3507 Fax: 410-614-8173. E.mail: jgrosse4@jhmi.edu. Web: http://www.hopkinsmedicine.org/DOM/TB_Lab/faculty/grosset.html

European Commission, DG Research
Dr Hannu Laang, Scientific officer, European Commission, DG Research, Unit F3 Infectious Diseases, rue du Champ de Mars 21, CDMA 2/161, B-1049 Brussels, Belgium, Tel.: + 32 2 296 96 02, Fax: 0032 2 299 45 E.mail: hannu.laang@ec.europa.eu Web: http://ec.europa.eu/research/