

source for most antibiotics on the market today, including the first-line and salvage TB regimens, including rifampin, streptomycin, amikacin and etc. A set of Microbial Natural Product Library (MNPL) containing secondary metabolites from a unique collection of actinomycetes and fungal strains from un- or under-explored ecological niches in China has been constructed. A pilot screen for potential anti-TB compounds was conducted with a selection of 5,000 extracts samples from this MNPL, utilizing a GFP labeled *M. bovis* BCG based HTS model ( $Z'$ -factor 0.8, CV < 15%, throughput 60,000 wells/day). 80 out of the 5,000 extracts showed >90% inhibition against logarithmically growing BCG were further evaluated on *M. tb* H37Rv strains at Broad Institute, as a dilution series ranging from 1× to 1/128×. The results showed that 46 extracts demonstrated anti-H37Rv activity, with 8 showing activity at 1/16×, and 1 showing activity at 1/128×. The following large scale fermentation and bioactivity guided compound isolation work lead to the discovery of diversified class of anti-TB compounds, including actinomycins (MIC 1–4 µg/ml), quinomycins (MIC 0.5 µg/ml), nanaomycins (MIC 8 µg/ml), cyclopeptides (MIC 2–8 µg/ml), anthraquinones (MIC 4–8 µg/ml), oligomycins, part of which were new compounds (not listed).

**OL-033** Etambutol-mediated changes in rat liver cytochrome P-450 isoforms expression and DNA-fragmentation processes

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**Objectives:** Etambutol is one of first-line antitubercular drugs in current therapeutic regimens. Its main disadvantage is wide spectrum of adverse effects which can lead to therapeutic failure. The aim of present study was to investigate etambutol effects on rat liver cytochrome P-450 isoforms expression and DNA-fragmentation processes.

**Methods:** Wistar albino male rats (160–200 g b.w.) were divided into two groups: I – received etambutol *per os* at a dose of 155 mg/kg b.w./day, II – control. After 60 days of the experiment, rats were sacrificed via cervical dislocation. Expression of rat liver CYP2E1, CYP3A2 and CYP2C23 were studied by RT-PCR methods. DNA fragmentation was investigated electrophoretically.

**Results:** Our data demonstrated etambutol-mediated quantitative and qualitative changes in male rat DNA fragmentation and expression of CYP2E1, CYP3A2 and CYP2C23 in comparison with control. CYP2E1 and CYP3A2 expression increasing was accompanied with CYP2C23 expression inhibition. DNA fragmentation processes were also greatly intensified at etambutol treatment. Its introduction caused appearance of new fractions with longer DNA-fragments (above 1000 b.p., 1000–800 b.p. and 800–600 b.p.). Among shorter DNA-fragments main fraction contained chains with 20–30 b.p.

**Conclusion:** Thus etambutol treatment caused adverse effects in organisms on the level of cytochrome P-450 isoforms expression and DNA-fragmentation processes. Extensive investigation of etambutol and cytochrome P-450 system interactions allowed to prevent or correct this antitubercular agent adverse effects.

**OL-034** A comparison study of extrapulmonary and pulmonary tuberculosis in Hong Kong

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**Background:** This study examines the differences between culture positive extrapulmonary and pulmonary tuberculosis

(TB) patients. It correlates these findings with the current understanding of extrapulmonary TB. It looks at how these factors affect mortality at six months and at the role of underlying diseases in drug resistance.

**Method:** This is a two year retrospective study comparing 115 extrapulmonary TB patients with 115 pulmonary TB patients.

**Results:** Extrapulmonary patients were younger than pulmonary patients with a median age of 53 years versus 73 years ( $p < 0.001$ ). They presented more commonly with lymphadenopathy ( $p < 0.001$ ). More extrapulmonary patients had chronic renal failure ( $p < 0.002$ ) and Human Immunodeficiency Virus (HIV) infection ( $p = 0.005$ ). They had a higher median erythrocyte sedimentation rate (61 mm/h vs. 48 mm/h,  $p = 0.017$ ), and lactate dehydrogenase level (309 U/L vs. 197 U/L,  $p = 0.006$ ). They had a lower median hemoglobin (10.7 g/dL vs. 11.7 g/dL,  $p = 0.002$ ), white blood cell count ( $7.4 \times 10^9/L$  vs.  $8.5 \times 10^9/L$ ,  $p = 0.039$ ), and lymphocyte count ( $0.9 \times 10^9/L$  vs.  $1.1 \times 10^9/L$ ,  $p = 0.051$ ).

There was no difference in mortality between extrapulmonary and pulmonary groups. Multivariate analysis identified age >60 years (Odds Ratio [OR] 2.4, 95% Confidence interval [95%CI] 0.98–5.77,  $p = 0.054$ ), presentation with decreased general condition (OR 3.5, 95%CI 1.46–8.34,  $p = 0.005$ ), hypertension (OR 2.7, 95%CI 1.16–6.38,  $p = 0.021$ ), radiological old TB (OR 2.6, 95%CI 1.25–5.52,  $p = 0.014$ ), and pleural effusion (OR 3.2, 95%CI 1.45–7.03,  $p = 0.004$ ) as independent risk factors for mortality.

9.1% of all cases had culture evidence of drug resistance. HIV infection ( $p = 0.001$ ) and intravenous drug usage ( $p = 0.001$ ) were the two risk factors identified.

**Conclusion:** There are important differences in demographics, clinical presentation and risk factors for extrapulmonary compared with pulmonary TB. Mortality is related to age and co-morbidity.

**OL-035** Tuberculosis disease burden in Southeast Asia

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**Objectives:** Tuberculosis, MTB or TB is the seventh leading frequent cause of death worldwide among infectious diseases. It is important to evaluate the current burden of disease, to know how this has been changing over time.

**Method:** Review of current literature.

**Result:** According to the WHO, an estimated about 9.2 million (139/100,000 population) new cases of TB occurred in 2006. Of these cases, 4.1 million (62/100,000 population) were new smear positive cases. There were 14.4 million (219/100,000 population) prevalent cases. There are 22 high-burden countries, but the majority of patients with TB live in the eight country of Asia; India, China, Indonesia, Bangladesh, Pakistan, Philippines, Vietnam and Afghanistan. India is the highest TB burden country in the world and accounts for nearly one-fifth (20%) of global burden of tuberculosis. In India, TB affects adults in the most productive age group (15–54 years). More than 80% of TB cases are in this group. TB kills almost 0.37 million Indian people every year with mortality rate of about 28/100,000 population. Globally, the case detection rate by DOTS programs increased almost linearly from 11% in 1995 to 28% in 2000, and then accelerated to 45% in 2003. The recent acceleration has been mostly due to rapid implementation in India, where case detection increased from 1.7% in 1998 to 47% in 2003, and in China, where it increased from 30% in 2002 to 43% in 2003. India and China together accounted for