**Date / Time:**
Tuesday, 14 September 2010
12.00 nn

**Venue:**
Microbiology Seminar Room
@ Level 3,
Department of Microbiology, MD4,
5 Science Drive 2
Singapore 117576

**Convener:**
Dr Justin Chu

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**“Drug Resistance and Bacterial Fitness in Mycobacterium Tuberculosis”**

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Since 2008, Dr Bifani has been working at the Novartis Institute for Tropical Diseases, Singapore. The focus of his present work is on TB hit-to-lead evaluation and target deconvolution. He obtained his PhD from the Sackler Institute, New York University, NY, USA and has been working on tuberculosis since joining the TB-Center at the Public Health Research Institute, New York (1994) where he characterized the outbreak multi-drug resistant strain W. Dr Bifani continued to work on TB at the Pasteur Institute, Lille, France (2000) where he also directed a project on Phage Therapy and was appointed Scientific Director of PhageGen (2001/4). In 2005 he formed and directed the laboratory of Molecular Pathology of Tuberculosis at the Pasteur Institute-Brussels until 2008. Past TB work have focused on TB-molecular epidemiology, drug resistance, mechanisms of drug resistance, TB animal models and drug development.

**Abstract**

Drug resistant isolates represent an alarming problem in TB control strategies. The WHO estimates that at least 50 million individuals worldwide harbor a MDR bacilli, defined as isolates resistant to at least isoniazid and rifampicin, the two most effective anti-tubercular drugs. Assessment of the global MDRTB threat has yielded a limited consensus on the magnitude of the problem and future trends. Some reports predict a global MDR-TB pandemic; while others see this trend as a local problem that can be managed through specific control strategies. One contributing factor affecting the predictions and outcome of the MDR-TB expansion is attributed to its heterogenic transmission success as a consequence of bacterial fitness. In pathogenic microorganisms, fitness can be a composite measure of an organism’s ability to survive, reproduce, and be transmitted. Noteworthy are the relative rates at which antibiotics-sensitive and resistant-pathogenic bacteria reproduce and die (compete) in the infected hosts, are transmitted in the host-populations and are cleared from infected hosts. The rate, nature and consequences of evolution of the cost of resistance can be studied in vitro by serial passages in axenic cultures or in vivo by utilizing cell cultures and animal models. In the present study we examine how mutations in the rifampicin-resistance-determining-region (RRDR), of the RNA-polymerase β-subunit; alters the bacillary fitness. Most rifampicin-resistance mutation comprise a single amino acid substitution in the RRDR. Rifampicin-resistant spontaneous mutants isogenic strains encoding mutations frequently encountered in clinical isolates were evaluated against those encoding mutations rarely found in clinical isolates. The fitness of the each mutant was evaluated through comparative survival and competitive experiments in DBA2 mice while transcriptional efficiency was determined by RT-PCR and microarrays analysis. The molecular constrains imposed on the mutated RNA-Polymerase protein were predicted by POP-analysis. Overall, common mutations were found to impose no constrains on the RNA Polymerase and accordingly were found to have no negative effect on bacterial fitness, while rare mutations had detrimental effects on bacterial survival. In in vivo experiments, common mutations out-competed rare and wild-type strains. This study helps in understanding the heterogeneity of drug-resistance fitness and could have a direct impact on treatment, patient care (isolation) and hence on the implementation of appropriate public health decisions when treating patients infected with rifampicin resistant strains.