

7th World Congress on

MICROBIOLOGY

November 28-29, 2016 Valencia, Spain



Patrick J Brennan

Colorado State University, USA

The cell envelope of *Mycobacterium tuberculosis* and new drug discovery against tuberculosis

Work of ours and others over the past 30 years has resulted in a thorough understanding of the structure of the mycobacterial cell wall and membranes but also the basic genetics and biosynthesis, providing essential targets for new drug development and molecular rationale for the bactericidal action of established antibiotics. The enzymology and underlying genetics of fatty acid and mycolic acids synthesis are well known and with it the mode of action of isoniazid, ethionamide, thiocaralides, thiolactomycin, etc. There is now convincing evidence that intercalated within this mycolic acids lipid environment are those 'special' (glycol) lipids; the phthiocerol dimycocerosates cord factor/dimycolyltrehalose, the sulfolipids, the phosphatidylinositol mannosides, etc., to form a true outer membrane (OM). Mycobacterial genetics and the creation of transposon and targeted mutant libraries has allowed definition of the synthesis of all of these entities, invaluable in comprehension of their roles in disease pathogenesis and aspects of the immune response; however, their general non-essentiality for bacterial growth limits their usefulness as targets for new drug development especially to counteract MDR-TB. The massive essential cell wall "core" of *M. tuberculosis* is comprised of peptidoglycan covalently attached via a linker unit (L-Rha-D-GlcNAc-P) to a linear galactofuran composed of Galp units, in turn attached to several strands of a highly branched arabinofuran (Araf), in turn attached to the mycolic acids. Definition of the genome of *M. tuberculosis* has greatly aided efforts to define the biosynthetic pathways leading to assembly of this cell wall core. Over the past 10 years we have painstakingly defined the essential enzymes in each of these pathways by knock-out and conditional mutagenesis and targeted the enzymes (e.g., all enzymes in the Rha synthetic pathway; the Galp mutase, the Galp and Araf transferases) by high and medium throughput screening of compound libraries. Yet, no promising leads have arisen from these efforts. Yet, the pursuit of interesting chemical entities by the research community, directly or via synthetic modifications has yielded some of the most promising lead compound now in our new drug armament. Examples are: the benzothiazinones, dinitrobenzamides and ethambutol inhibiting aspects of arabinan synthesis; CPZEN-45 inhibiting synthesis of the linker unit; the diarylquinolones and benzophenones addressing electron transport; thioureas inhibiting aspects of fatty acid synthesis; substituted triclosan derivatives and the nitroimidazoles inhibiting aspects of mycolic acids synthesis and several diamines involved in inhibition of the translocation of mycolic acids. These developments and others will be discussed in the context of current approaches to exploit our unprecedented knowledge of the biogenesis of the cell wall and membranes of *M. tuberculosis* for purposes of producing new and safe chemical scaffolds to address tuberculosis in its various aspects.

Biography

Patrick J Brennan was graduated from University College Cork, National University of Ireland with the degrees of BSc (1961) and MSc (1962) before arriving at Trinity College Dublin to undertake research, leading PhD degree (1965), on the mode of action of the anti-tuberculosis drug, Isoniazid, followed by a two year Postdoctoral Fellowship at the University of California (Berkeley) studying the structures and biosynthesis of the phosphatidylinositol mannosides of *Mycobacterium tuberculosis*. He has held Senior posts in the National Jewish Centre for Immunology and Respiratory Medicine and the University of Colorado, School of Medicine in Denver before being appointed as Associate Professor, Professor and ultimately University Distinguished Professor at Colorado State University. He has published more than 300 peer reviewed papers on tuberculosis and leprosy. He has served as Chairman of the World Health Organization Program for Tropical Disease Research; Research Advisor to the Sasakawa Memorial Health Foundation who, through the Nippon Foundation, underwrites most of the Global Leprosy Elimination Campaign and Chairman of the US-Japan Cooperative Medical Sciences Program.

Patrick.Brennan@ColoState.EDU