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Frontiers in Chemistry Lecture Series

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Targeting mycolic acid biosynthesis and export in Mycobacterium tuberculosis

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WO 1205

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Abstract
The presentation will briefly review the TB drug discovery efforts that have led to a renewed interest in compounds targeting cell envelope biogenesis in the last 5 years. It will further describe recent efforts in the investigator's laboratory that have led to the identification of novel targets in the essential mycolic acid biosynthetic pathway.

Biography
Dr. Mary Jackson, a native of France, received a Master of Science Engineering degree in 1994 from the National School of Agronomy in Rennes, France where she studied biochemistry and genetics. She received her Ph.D. from the Pasteur Institute in Paris in 1998. After one year as a postdoctoral fellow at Colorado State University, she returned to the Pasteur to work as a Research Scientist focusing on mycobacterial genetics. One year later, she became an Assistant Professor at the Pasteur. In 2007, she was recruited back to Colorado State University where she has continued her mycobacterial work. In 2009, she was made the Associate Director of the Mycobacterial Research Laboratories and became Director of the MRL in 2012.

Dr. Jackson is known for her extensive work on Mycobacterium tuberculosis using primarily gene knockout studies and whole-cell assays to identify and characterize mycobacterial drug targets. Her current and long-term research interests focus on the genes and proteins responsible for mycobacterial cell wall biosynthesis. Of note are two aspects of her recent work. First, she identified the plasma membrane embedded MmpL3 protein as the transporter of trehalose monomycolate across the bacterial membrane (Nature Chemical Biology 2012). Since, trehalose monomycolate transport is essential for the viability of M. tuberculosis, MmpL3 is now a major drug discovery target in M. tuberculosis with multiple drugs now in clinical trials that target MmpL3 activity. Second, she identified two fatty acid dehydratase enzymes as the targets of two anti-tuberculosis drugs, thiacetazone and isoxyl (J. Biological Chemistry 2011), and is actively researching the mechanism of action.

Selected Publications

1) Pelicic, V., Jackson, M., Reyrat, J.-M., Jacobs Jr., W. R., Gicquel, B. and C. Guilhot (1997) Efficient allelic exchange and transposon mutagenesis in *Mycobacterium tuberculosis*. *Proc. Natl. Acad. Sci USA*, 94, 10955-10960.
2) Sulzenbacher, G., Canaan, S., Bordat, Y., Neyrolles, O., Stadthagen, G., Roig-Zamboni, V., Rauzier, J., Maurin, D., Laval, F., Daffé, M., Cambillau, C., Gicquel, B., Bourne, Y., and Jackson, M. (2006) LppX is a lipoprotein required for the translocation of phthiocerol dimycocerosates to the surface of *Mycobacterium tuberculosis*. *EMBO J.* 25: 1436-1444.

3) Kaur, D., Obregón-Henao, A., Pham, H., Chatterjee, D., Brennan, P.J., and Jackson, M. (2008) Lipoarabinomannan of *Mycobacterium*; mannose capping by a multifunctional terminal mannosyltransferase. *Proc. Natl. Acad. Sci. USA* 105: 17973-17977.

4) Christophe, T., M. Jackson, H. K. Jeon, D. Fenistein, M. Contreras Dominguez, J. Kim, A. Genovesio, J.-P. Carralot, F. Ewann, E. H. Kim, S. Y. Lee, S. Kang, M. J. Seo, E. J. Park, H. Škovierová, H. Pham, G. Riccardi, J. Y. Nam, L. Marsollier, M. Kempf, M.-L. Joly-Guillou, T. Oh, W. K. Shin, Z. No, U. Nehrbass, R. Brosch, S. T. Cole, and P. Brodin. (2009). High content screening identifies decaprenyl- phosphoribose 2' epimerase as a target for intracellular antimycobacterial inhibitors. *PLoS Pathog*. 5(10):e10000645.

5) Grzegorzewicz, A. E., H. Pham, V. A. K. B. Gundi, M. S. Scherman, E. J. North, T. Hess, V. Jones, V. Gruppo, S. E. M. Born, J. Korduláková, S. S. Chavadi, C. Morisseau, A. J. Lenaerts, R. E. Lee, M. R. McNeil, and M. Jackson (2012) Inhibition of mycolic acid transport across the *Mycobacterium tuberculosis* plasma membrane. *Nat. Chem. Biol.* 8(4): 334-341.

6) Favrot L., Grzegorzewicz A. E., Lajiness D. H., Marvin R. K., Boucau J., Isailovic D., Jackson M., Ronning D. R. (2013). Mechanism of inhibition of *Mycobacterium tuberculosis* antigen 85 by ebselen. *Nat Commun* 4: 2748.

Frontiers in Chemistry Lecture Series
The Department of Chemistry's Frontier's in Chemistry Lectureship Series was inaugurated in 1984 with a lecture by George S. Hammond. The series has remained active with lectures each year since, including chemistry Nobelists H. C. Brown, R. H. Grubbs, E. Negishi, and H. A. Hauptman. The "Frontiers" lecturers have also included Al Cotton, Alan Fersht, Tom Kaiser, Sid Hecht, Ron Breslow, Ken Houk, JoAnne Stubbe, Mike Marletta, John Arnold, Bill Roush and Steve Benkovic. The lecture series is sustained by an endowed fund that was initiated by donations from University of Toledo chemistry faculty members dating back to 1981.