UKEIRI Project Review Meeting

August 23rd 2013

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INDIAN INSTITUTE OF SCIENCE

BANGALORE

Genesis of the Proposal

Research activities led to questions related to expertise available in UoB

Visit to UoB by graduate student from IISc while participating in a Royal Society Grant between Dr. Roger Buxton (NIMR, London) and Prof. Visweswariah (IISc)

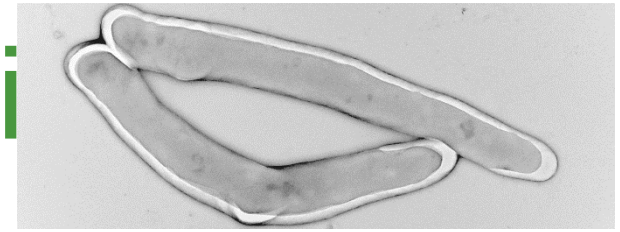
Visit and seminar presented in UoB

Joint discussions

Funds allocated in UoB for greater exchange and interaction between UoB and Indian Universities

Visits of UoB faculty to IISc-joint One-Day Symposium held in Sept 2011

Novel Approaches to Tackli Tuberculosis



Project Title : Novel Approaches to Tackling Tuberculosis

Start Date : June 2012

End Date : May 2014

UK Lead Institution Name: School of Biosciences, University of Birmingham

UK Project Leader: Dr. Apoorva Bhatt (MRC Fellow and Lecturer) Dr. Peter Lund (Reader)

UK Postal Address : School of Biosciences Edgbaston, Birmingham B15 2TT

Indian Lead Institution Name: Indian Institute of Science, Bangalore

Indian Project Leader: Professors V. Nagaraja and Sandhya S. Visweswariah

India Postal Address : Dept. of Microbiology and Cell Biology; Dept. of Molecular Reproduction, Development and Genetics, Indian Institute of Science CV Raman Avenue,Bangalore, 560012 Karnataka, India

Objectives of the Proposal

1) Interplay between central metabolism and cell wall composition.
   - Bhatt and Besra (UoB) Visweswariah (IISc)

2) The role of nucleoid associated proteins in global regulation.
   - Busby (UoB) Nagaraja and Chatterji (IISc)

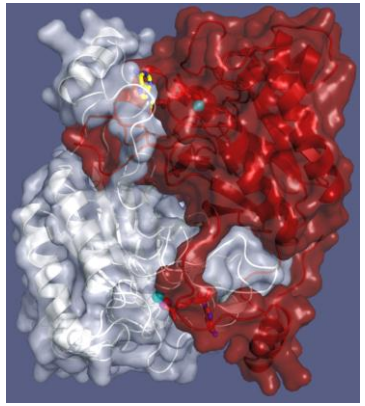
3) Novel technologies to study proteins involved in sensing environmental stimuli.
   - Lund (UoB) Saini (IISc)

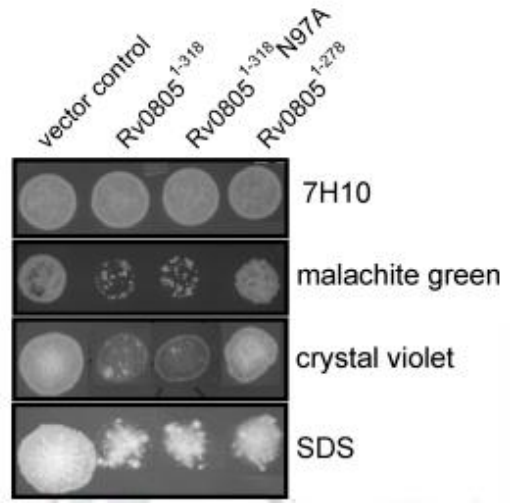
4) Evaluation of a diagnostic tool based on spectroscopic detection of a lipid biomarker.
   - Bhatt and Besra (UoB) Umapathy and Saini (IISc)

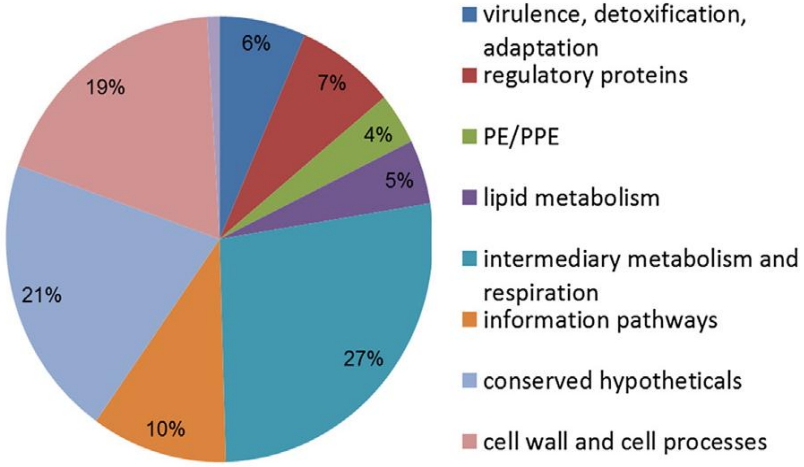
Interplay between central metabolism and cell wall composition

Role of cAMP in regulating the cell wall in mycobacteria

- Shenoy A.R. and **Visweswariah, S.S.** New Messages from Old Messengers: cAMP and Mycobacteria. *Trends Microbiol*. 14: 543-550
- Shenoy A.R., Sreenath, N., Podobnik, M., Kovacevic, M., **Visweswariah, S.S.** The Rv0805 gene from Mycobacterium tuberculosis encodes a 3',5'-cyclic nucleotide phosphodiesterase: biochemical and mutational analysis. *Biochemistry.* 2005 44:15695-704.
- Podobnik, M., Tyagi, R., Matange, N., Dermol, U., Gupta, AK., Mattoo, R., Seshadri, K. and **Visweswariah, S.S**. (2009) A mycobacterial cyclic AMP phosphodiesterase that moonlights as a modifier of cell wall permeability *J. Biol. Chem.* 284: 32846–32857
- Matange, N., Hunt, D.M., Buxton, R. S. and **Visweswariah, S.S**. (2013) Overexpression of the Rv0805 phosphodiesterase elicits a cAMP-independent transcriptional response. *Tuberculosis* 93: 492-500







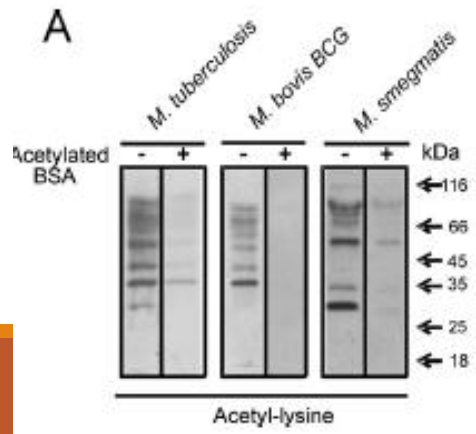
Interplay between central metabolism and cell wall composition *cont…*

Cyclic AMP, protein acetylation and fatty acid metabolism in Mycobacteria

Nambi, S., Basu, N. and **Visweswariah, S. S.** (2010) Cyclic AMP-regulated protein lysine acetyl transferases in Mycobacteria. *J. Biol. Chem.* 285:24313-2432

Nambi, S, BadiReddy, S, **Visweswariah, S.S.** and Anand, GS (2012) Cyclic AMP-induced Conformational Changes in Mycobacterial Protein Acetyltransferases. *J. Biol. Chem.* 287:18115-29

Nambi, S., Gupta, K., Bhattacharya, M., Ramakrishnan, P., Ravikumar, V., Siddiqui, N., Thomas, A.T. and **Visweswariah, S.S**. (2013) Cyclic AMP-dependent protein lysine acylation in mycobacteria regulates fatty acid and propionate metabolism**.** *J. Biol. Chem.* 288:14114-14124



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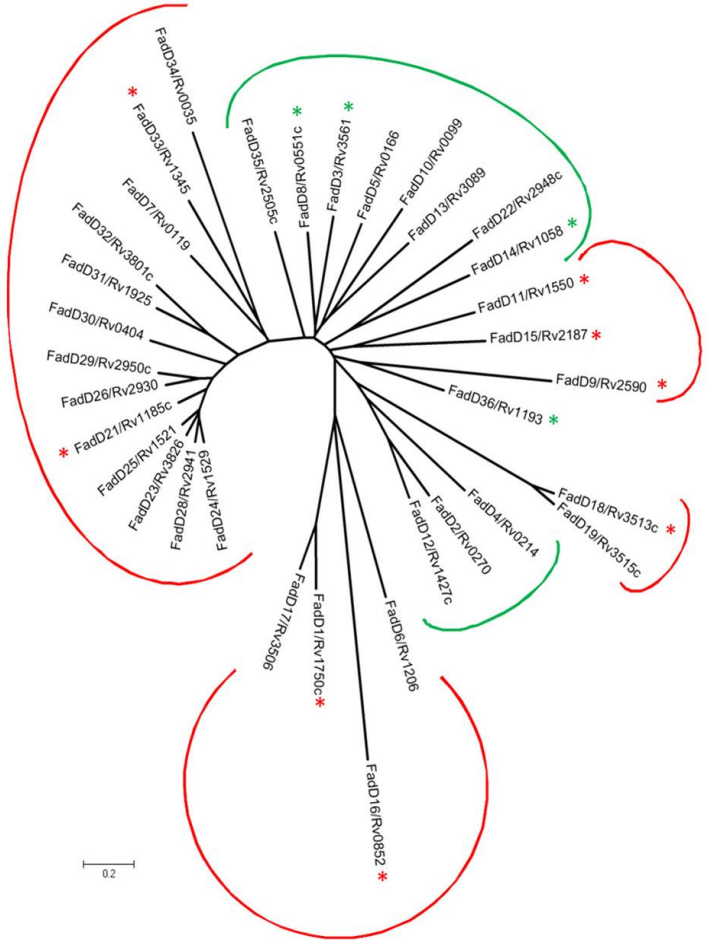


Exchange visits (2012-current)

Dr. Subhalaxmi Nambi-former PhD student and post doctoral fellow

- Hosted by Dr. Bhatt and Prof. Besra (UoB) for training in the extraction and analysis of mycobacterial lipids in Feb-March 2013. Duration of stay 1 month.

Prof. Visweswariah also visited UoB at a later date towards the end of February.

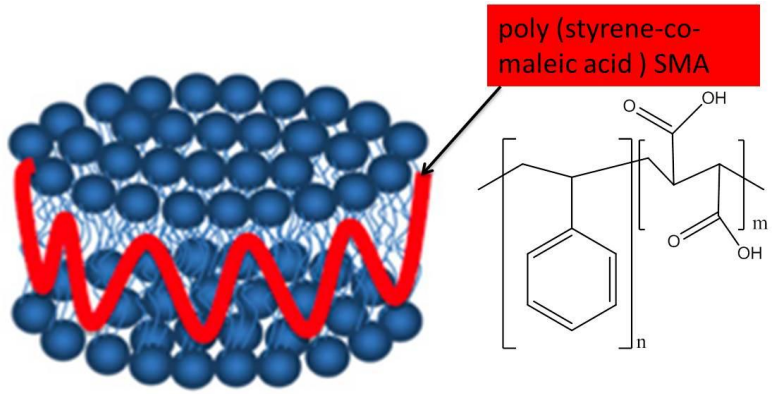
- Discuss future plans and approaches; take stock of results (duration of stay 1 week)

Deepak K Saini (IISc)

VISIT TO LABORATORIES OF
LUND AND BHATT, UoB, APRIL 15 – 29TH 2013.

Develop methods to study two-component systems in *M. tuberculosis.*

- Nanodisc technology was performed in Prof. Lund's laboratory for PhoQ sensor kinase of E. coli. This method allows reconstitution of membrane proteins into soluble membrane like disks for downstream studies. *Technology was developed in the lab of Prof. Tim Dafforn, UoB with whom Prof. Lund collaborates.*
- The long term objective is to study the bioactivities of various full length sensor kinases of *M. tuberculosis* in nanodisc platform.
- Work towards this has been initiated in the Saini laboratory.



Utilization of mycolic acid signatures to identify of mycobacterial species

- Methodology of mycolic acid extraction learnt (to be performed in Saini laboratory)
- Mycolic acid (FAMEs and MAMEs) were isolated from *M. smegmatis* for utilization as standards for detecting mycolic acid signatures using spectroscopic techniques.
- Spectroscopy work underway in Umapathy and Saini laboratories.
- Isolated lipids and mycolic acids were shipped to Saini laboratory for IR spectroscopy analysis.

Proposed visits (present – June 2014)

Prof. Steve Busby-October 2013 (Nagaraja and Chatterji laboratories)

Drs. Bhatt and Besra-early 2014 (Visweswariah and Saini laboratories)

March-May 2014-Nagaraja, Chatterji, Visweswariah, Saini visits (finalize joint publications)

March-April 2014-Post doctoral fellow from Visweswariah Laboratory to UoB

The way forward

Press : http://articles.timesofindia.indiatimes.com/2011-12-26/news/30558435_1_anti-tb-drug-treatment-cocktail-of-four-drugs

The best approach to sustain the research links formed as part of this thematic proposal is to apply for research grant funding, ideally for each subtheme.

Research funding bodies in the UK now allow overseas institutions/individuals to be partners in research grants.

The first step towards laying a strong foundation for such joint grants has already been achieved by the grant of this thematic partnership. The other key component, joint publications, seems feasible in a year's time in at least some of the sub-themes.

We envisage two sub-projects to progress to this next stage for funding from the Medical Research Council (UK):

1) Interplay of secondary metabolism and cell wall assembly.

2) Spectroscopic detection of lipid biomarkers and a diagnostic tool for TB