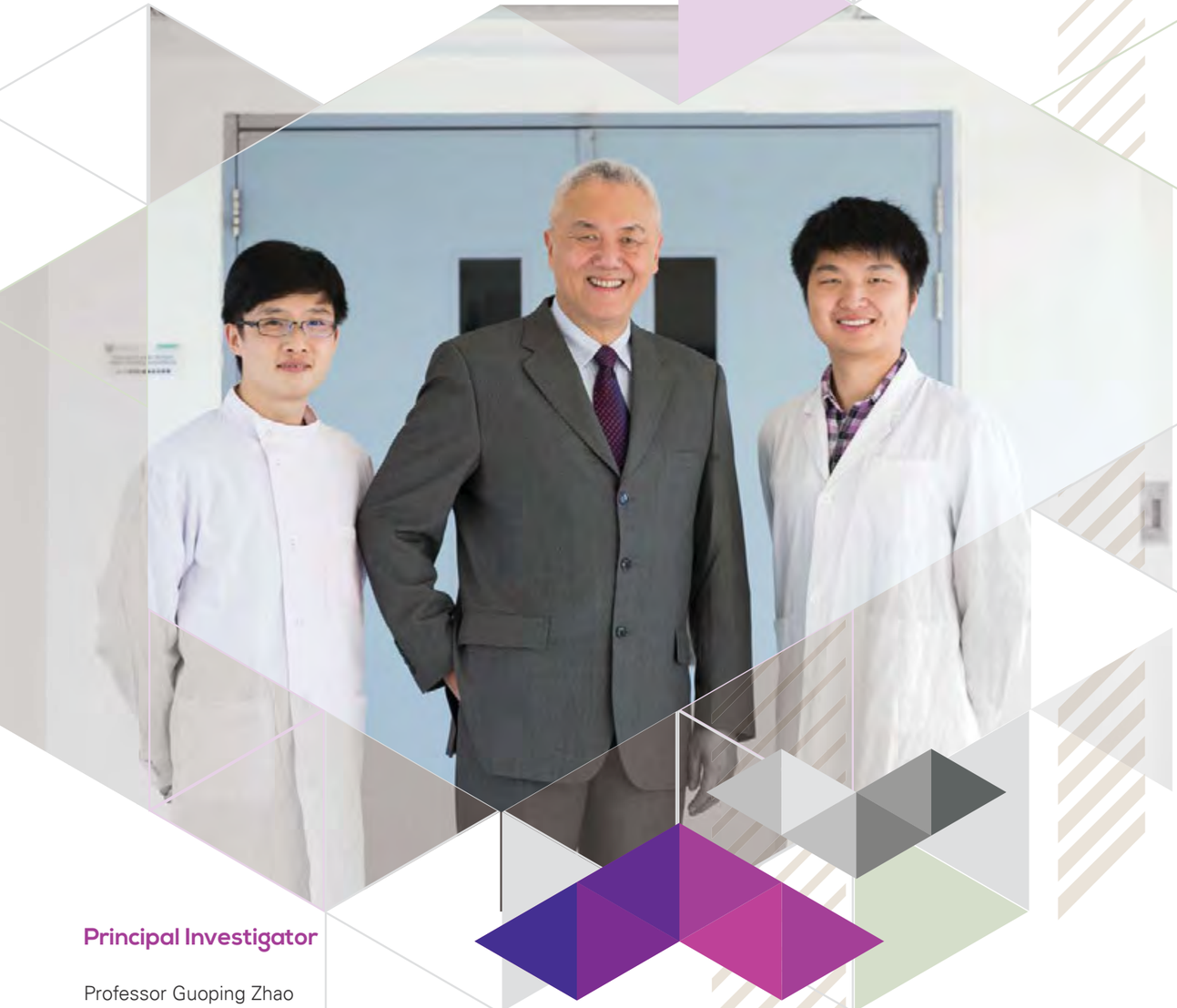
07
MOLECULAR MICROBIOLOGY
(Clinical Microbial Genomics)



Principal Investigator

Professor Guoping Zhao

Team

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Research Progress Summary

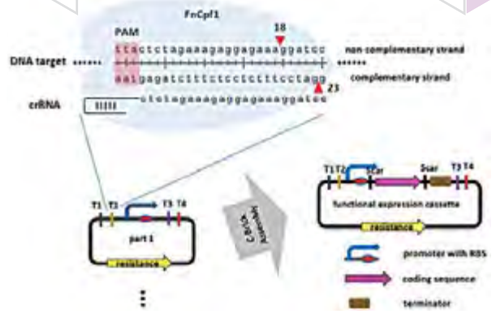
Mycobacterium tuberculosis (*Mtb*), the causative agent of tuberculosis, is an extraordinary human pathogen that has latently infected one-third of the world population and causes 9 million new cases and about 1.5~2 million deaths each year worldwide.

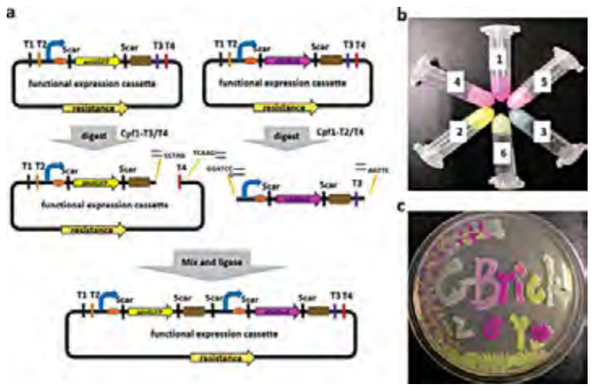
Studies by Professor Guoping Zhao and his team demonstrated that mycobacterial MazG is a 5-OH-dCTP-specific housecleaning enzyme involved in a pathway preventing the CG to TA mutation and ensuring the persistent infection of *Mtb* in mouse (PLOS Pathog 9:e1003814. 2013). A recent study showed that mycobacterial MazG is required for *Mtb* multidrug tolerance through prevention of 5-OH-dCTP-induced double-strand DNA breaks (to be submitted). In addition, the team also found that the human DCTPP1 (MazG homolog) attenuates the sensitivity of human gastric cancer cells to 5-fluorouracil (Oncotarget 7(42): 68623-68637. 2016).

In order to understand the mechanism of persistence infection of *Mtb*, molybdenum cofactor (MoCo) biosynthesis genes, particularly, the characteristics of the multiple-copy genes, specially found in *Mtb* but different from that of *E. coli* or even *Mycobacterium smegmatis* (*Msm*), have been under investigation. Interesting and novel discoveries have been observed via site-directed mutation experiments and corresponding biochemical and physiological mechanisms are being analysed.

In addition, aiming at understanding the critical survival mechanism of *Mtb* under hypoxia dormancy state, nitrate metabolism of both *Msm* and *Mtb* are studied via systematic comparison the related *Mtb* physiology against that of either physiologically phenocopied or genetically manipulated *Msm* models. Recent progresses were achieved in identification and characterisation of novel nitrate metabolism mechanisms in *Msm* besides the well-studied NarGHJI-dependent nitrate assimilation system.

Complete genome sequencing of 5 Beijing lineage strains of *Mtb* revealed the presence of a novel region of difference (RD) of ~4kb, which is absent from other completely sequenced MTBC genomes and designated M-NBjD1. Its potential impact in both physiology/pathology and evolutionary is under investigation. In order to facilitate the molecular manipulation of mycobacterial genomes, which has been the rate-limiting step for the research of the field, development of synthetic biology enabling technology, particularly the CRISPR/Cas9 related techniques, has been a new direction of the laboratory.



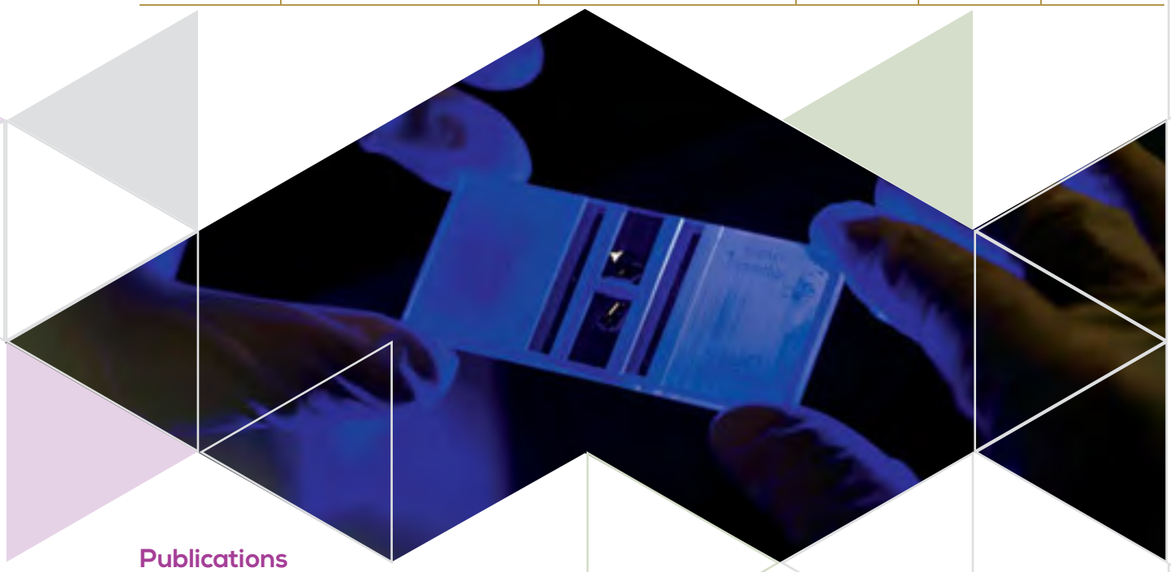


Schematic diagram of the Cpf1/crRNA/DNA target complex (top) and the colorful bacterial pigments produced by *E. coli* harboring constructs assembled in C-Brick standard (bottom a and b).
C-Brick: A New Standard for Assembly of Biological Parts Using Cpf1

Recognitions

Grants and Consultancy

Full Name of PI	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Guoping Zhao	結核分枝桿菌的模式菌株恥垢分枝桿菌新型硝酸還原酶的鑒定	The National Natural Science Foundation of China	01/01/2017	31/12/2020	RMB 800,000



Publications

A. Journal Papers

1. Han X, Shen L, Wang Q, Cen X, Wang J, Wu M, Li P, Zhao W, Zhang Y, Zhao G. Cyclic AMP Inhibits the Activity and Promotes the Acetylation of Acetyl-CoA Synthetase through Competitive Binding to the ATP/AMP Pocket. *Journal of Biological Chemistry*. 2016; 292(4):1374-84.
2. Dong H, Zhou B, Kang H, Jin W, Zhu Y, Shen Y, Sun J, Wang S, Zhao G, Hou J, He Y. Small surface antigen variants of HBV associated with responses to telbivudine treatment in chronic hepatitis B patients. *Antiviral Therapy*. 2017; 22(1):43-51.
3. Wang X, Tang B, Ye Y, Mao Y, Lei X, Zhao G, Ding X. Bxb1 integrase serves as a highly efficient DNA recombinase in rapid metabolite pathway assembly. *Acta Biochimica et Biophysica Sinica*. 2016; 49(1):44-50.
4. Xia L, Tang Y, Song F, Xu L, Ji P, Wang S, Zhu J, Zhang Y, Zhao G, Wang Y, Liu T. DCTPP1 attenuates the sensitivity of human gastric cancer cells to 5-fluorouracil by up-regulating MDR1 expression epigenetically. *Oncotarget*. 2016; 7(42):68623-37.
5. Li S, Zhao G, Wang J. C-Brick: A New Standard for Assembly of Biological Parts Using Cpf1. *ACS Synthetic Biology*. 2016; 5(12):1383-8. (Letter)