NANYANG TECHNOLOGICAL UNIVERSITY

School of Biological Sciences

Reg. No. 200604393R

Research Theme: Synthetic biology

Research Project Title: Production of cannabinoids and other natural products using microbial hosts

Principal Investigator/Supervisor: Liang Zhao-Xun

Co-supervisor/ Collaborator(s) (if any): NA

Project Description

a) Background:

Streptomyces is a genus of filamentous actinobacteria renowned for the capability to produce secondary metabolites. A small number of *Streptomyces* strains have also been exploited as heterologous hosts for the production of commercially valuable compounds. Our lab recently isolated hundreds of actinobacteria strains from the tropical soil and marine environment of Singapore, with the original aim of discovering microbes that produce novel secondary metabolites. Two *Streptomyces* strains in our collection not only possess a large number of biosynthetic gene clusters, but exhibit faster growth than typical *Streptomyces* strains. Given their biosynthetic capability, fast-growing property and amenability to genetic manipulation, the two *Streptomyces* strains have the potential to become versatile proprietary heterologous hosts. Here we propose a project to explore the two *Streptomyces* strains as microbial heterologous hosts for producing cannabinoids and other terpenoids. Cannabinoids are a small class of plant secondary metabolites produced by a polyketide-terpene hybrid pathway in cannabis plants. Cannabinoids have long been recognized for their therapeutic values in relieving chronic and neuropathic pain. Several cannabinoids are currently at different stages of clinical development for various medical applications. Developing a platform for producing cannabinoids by microbial fermentation will allow us to bypass the cultivation of heavily controlled cannabis plants and the lengthy process of extracting cannabinoids from plant material. We will employ the latest genome-editing and synthetic biology tools to optimize the *Streptomyces* hosts; and we will build *de novo* designed cannabinoid biosynthetic gene cassettes to produce cannabinoids using the *Streptomyces* heterologous hosts.

We expect the Ph.D. candidate to develop analytical skill and technical expertise in 1) developing proprietary heterologous hosts and generating genetic tools for manipulating microbial genome and biosynthetic pathways; 2) producing commercially valuable cannabinoids and new structural derivatives at reduced cost; 3) developing synthetic biology tools required for genome editing and *de novo* design of biosynthetic pathways.

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b) Proposed work:

1. Characterization, assessment and optimization of the proprietary Streptomyces strains as heterologous hosts. After genome sequencing, genome editing will be performed to improve genome stability and delete competing biosynthetic pathways. We will also identify and validate DNA promoters needed for tuning gene expression in the Streptomyces hosts.
2. Construction of de novo designed cannabinoid biosynthetic gene cassettes and production of cannabinoids by heterologous expression. We will design and assemble cannabinoid biosynthetic gene cassettes and optimize the expression of individual biosynthetic genes. Fermentation and gene expression will be optimized systematically to improve the production of cannabinoids.
3. Production of other terpenoids by heterologous expression using the optimized heterologous hosts. We will mine genome database for novel terpene biosynthetic gene clusters. The chosen clusters will be cloned and refactored to be expressed in the hosts/

Supervisor contact:

If you have questions regarding this project, please email the Principal Investigator:

SBS contact and how to apply:

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Please apply at the following:

http://admissions.ntu.edu.sg/graduate/R-Programs/R-WhenYouApply/Pages/R-ApplyOnline.aspx