Research Theme: **Molecular Biology or Developmental Neuroscience**

PhD Research Project Title:

Decoding the Genetic Landscape of Human Brain Expansion

Scholarship category (Please indicate the source of funding for this project):

SBS Research Student Scholarship

Principal Investigator/Supervisor: **Richard She**

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

Project Description

a) Background:

The 3-fold expansion of the human cerebral cortex is perhaps the most defining feature of our evolution. This dramatic increase in brain size, which unfolded over just a few million years, enabled the emergence of language, abstract reasoning, and complex culture. But despite the scale of this transformation, we still don't know which genes or pathways actually drove it.

Comparing humans to our closest relatives—the great apes—offers a powerful way to approach this question. Chimpanzees share more than 98% of our DNA, yet differ in fundamental ways, not just in brain size, but in developmental timing, lifespan, and cognition. Evolutionary differences between species are encoded in the genome, but we still lack a systematic method to link those genetic differences to cell-level behaviors.

Our lab uses stem cell–derived brain organoids to bridge that gap. These 3D tissue models allow us to grow human and chimpanzee neural tissue side by side in a dish. By perturbing genes across the genome, we can ask which ones actually influence developmental programs—causing cells to divide more, mature more slowly, or behave differently in one species but not the other.

Rather than relying solely on gene expression or sequence comparisons, our goal is to directly test function. What happens when you knock out a gene? Does it change how neural progenitors grow and divide? And are the consequences of that perturbation the same in humans and chimps?

b) Proposed work:

Incoming Ph.D. students will lead a genome-wide CRISPR screen to identify the genetic changes that contributed to human brain expansion. This project combines cerebral organoid models, cross-species functional genomics, and high-throughput single-cell analysis. It is designed for early student ownership and is structured to yield publishable findings within a standard Ph.D. timeline.

Project: A functional atlas of gene-by-species effects on early cortical development

We begin by differentiating induced pluripotent stem cells (iPSCs) from humans and chimpanzees into cerebral organoids. These models faithfully capture key events in early brain development—including neural progenitor expansion, neurogenesis, and the emergence of layered cortical structure.

Using a genome-wide CRISPRi library with guides matched across the human and chimpanzee genomes, we will perturb nearly every gene in the genome in parallel. After 35 days of organoid maturation, we will use fluorescence-activated cell sorting (FACS) to isolate distinct cell populations, focusing on neural progenitors and post-mitotic neurons.

For each sgRNA, we measure its enrichment or depletion in each population. Genes whose depletion enhances the renewal potential of progenitor cells will be overrepresented in the progenitor fraction and underrepresented in the neuron fraction. Genes that promote differentiation or cell cycle exit will show the opposite pattern. By comparing these effects across species, we can identify which genetic dependencies are conserved—and which have shifted during human evolution.

This project will generate a functional map of how individual genes influence developmental dynamics in a species-dependent way. Top candidates will be prioritized for follow-up using focused perturbation, transcriptomic profiling, and validation in additional great ape species.

Students in this project will gain deep training in stem cell differentiation, pooled CRISPR screening, and FACS. This work sits at the intersection of evolution, development, and systems biology—and offers a unique opportunity to discover how molecular changes gave rise to human-specific traits.

c) Preferred skills:
Scientific curiosity and motivation are essential. Prior experience with mammalian cell culture, CRISPR editing, or computational analysis is helpful but not required. Students from biology, bioengineering, or quantitative backgrounds are all encouraged to apply.

Supervisor contact:

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SBS contact and how to apply:

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Please apply at the following:

Application portal:

https://venus.wis.ntu.edu.sg/GOAL/OnlineApplicationModule/frmOnlineApplication.ASPX