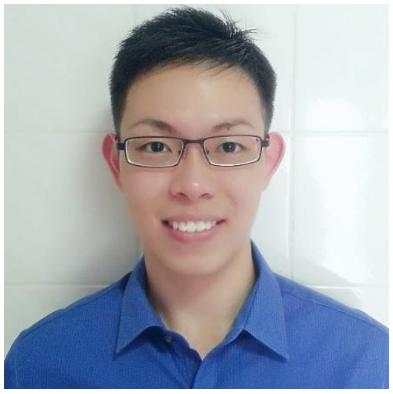
CHEMICAL ENGINEERING

DISTINGUISHED YOUNG SCHOLARS SERIES



ANDY TAY KAH PING

Monday, July 30, 2018

Postdoc
Stanford University

Nano and Micro Tools for Directed Cell Evolution

ABSTRACT: 'Summer's coming! Come join our fitness classes and get a beach-ready bod!' reads the advertisement from the school gym. For many, including myself, gyms are facilities where we train and evolve our bodies to better withstand environmental stresses such as squeezing into a rush-hour bus. Cells respond to external stimuli just like us! Cancer cells, for instance, can evolve to tolerate higher mechanical stresses to squeeze through tiny capillaries during metastasis. In this seminar, I will present the various 'gyms' I have built to condition or evolve cells with desirable biomechanical/magnetic properties for biomedical applications.

Mechanical conditioning of neurons for pain modulation: In the 1950-60s, scientists found that biomechanical forces regulate brain development but the discovery of DNA and genetic code shifted attention away from this area. Through my work, I sought to illustrate the impact of biomechanics on cellular developments and build on knowledge in mechanobiology to design innovative clinical therapies.

I have shown that the use of micro-fabricated magnetic substrates with membrane-bound magnetic nanoparticles can mechanically stimulate neurons to induce Ca2+ influx through excitatory mechano-sensitive N-type Ca2+ channels (Tay et al., ACS Nano, 2016). It is known that neurons maintain network activity homeostasis by actively regulating their ratio of excitatory and inhibitory protein ion channels. Simply, this means repeated stimulation causes reduction in excitatory channels expression and vice-versa. I found that chronic magneto-mechanical stimulation in a Fragile X Syndrome (FXS) neuronal model reduced the over-expression of N-type Ca2+ to restore healthy synaptic transmission (Tay et al., Nano Letters, 2017, Fig. 1A).

Unfortunately, the GPa stiffness of the magnetic substrate was incompatible with stimulation of soft brain/ spinal cord tissues (~100 Pa). This motivated me to develop a magnetic hyaluronic acid hydrogel that shares similar biochemical/physical properties as the extracellular matrix of the brain/spinal cord. The gel facilitated healthy growth of neurites and mature ion channel expressions (Tay et al., Adv Mat, 2018). Tests with neuro-toxins and electrophysical recordings revealed that acute magneto-mechanical stimulation induced Ca2+ influx in spinal cord dorsal root ganglion (DRG) neurons via endogenous, mechano-sensitive TRPV4 and PIEZO2 channels (Fig. 1B). Next, capitalizing on the homeostatic tendencies of neural networks, I performed chronic magneto-

mechanical stimulation and found that it reduced the expression of PIEZO2 channels. These results support that neurons can be mechanically conditioned to modulate their responses to mechanical stresses, potentially providing relief to pain where PIEZO2 channels are typically over-expressed.

Directed evolution of magnetotactic bacteria (MTB): MTB are a unique class of prokaryotes that naturally crystallize ferromagnetic iron-oxide magnetic nanoparticles (MNPs) with homogenous shapes, sizes and magnetic properties. Consequently, there is significant interest to exploit MTB as bio-factories for producing MNPs. Despite advances in gene editing techniques, it is challenging to generate MTB over-producing MNPs with uniform properties or confer biomagnetic properties to other bacteria strains. In my work, I established a mutation-selection protocol where I combined random chemical mutagenesis and selection using a magnetic ratcheting system to create a library of MTB mutants with different magnetic contents (Tay et al, Adv Funct Mat, 2017, Fig. 1C). Mutants without MNPs allowed us to identify the minimum gene set for biomineralization (mamB, mms6) while over-producer mutants were used to generate MNPs for biomedical use in cancer hyperthermia. I next built a high-throughput microfluidic platform compatible with industrial bioreactor for large-scale magnetic sorting and culture of MTB over-producer mutants (Tay et al., Under Revision).

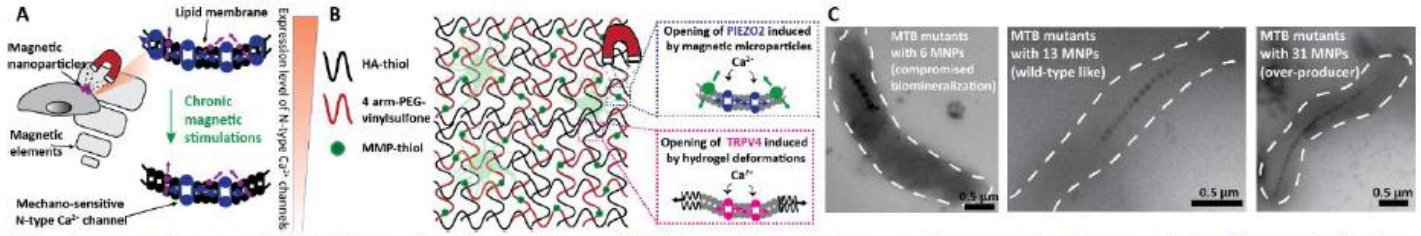


Fig. 1 'Gyms' or tools for directed cell evolution. (**A**) Magnetic substrate and magnetic nanoparticles for modulating mechano-sensitive N-type Ca^{2+} channels. (**B**) Magnetic hyaluronic acid hydrogels for potential pain relief through chronic magneto-mechanical stimulation. (**C**) A library of MTB mutants with different magnetic contents.

BIOGRAPHY: Andy Tay graduated in 2014 from the National University of Singapore (NUS) with a First Class Honors in Biomedical Engineering (B. Eng). He went on to receive the NUS-Overseas Graduate Scholarship for his PhD in the University of California, Los Angeles where he recently graduated (2017) with his thesis on non-invasive neural modulation. He has received multiple academic awards including the prestigious Helmsley Fellowship (Cold Spring Harbor Laboratory), Toshihiko Tokizane Memorial Award for Excellent Graduate Study in Neuroscience, SciFinder® Future Leaders Program (American Chemical Society) and Materials Research Society Postdoctoral Publication Prize.

Andy is also highly passionate in science communications and have published articles with Naturejobs Blog, Science and The Scientist among others. For his commitment in evidence-based science communication, he has received the Highly Commended Runner-Up for the Queen's Young Leader Award, Travel Fellowship from Universcience (the largest European science museum) and a Visiting Fellowship from the Museum of Arts and Sciences Sydney.

Andy is currently undergoing his postdoctoral training in Stanford University with the support of the NUS-Overseas Postdoctoral Fellowship where he is developing nanotechnology for controlling stem cell lineage.

LECTURE 4:00 - 5:00 (PAA) A110
Happy Hour in Benson Hall Lobby Following

CHEMICAL ENGINEERING
UNIVERSITY of WASHINGTON
Knowledge and solutions for a changing world