In the second issue of the NUHS Research Bulletin, besides providing updates about recent research advances within our NUHS community, we have included a New Faculty Feature, which aims to introduce the research interests of our new faculty members.

**Internal cerebral vein asymmetry as a potential predictor of poor functional outcome in stroke patients treated with thrombolytic therapy**

Although many patients with acute ischemic stroke are successfully treated with thrombolytic therapy, some do not respond as well. Predicting which patients are more prone to poor outcomes helps clinicians and patients plan for rehabilitation after treatment. Finding new prognostic factors could help to improve these predictions. One such factor, the presence of asymmetric internal cerebral veins (ICV), was recently reported by Dr Vijay Sharma and colleagues.

ICV are a pair of prominent veins that run parallel and very close to each other, draining deep parts of the brain. In normal brains, the veins have a consistently symmetrical appearance in computed tomography angiography (CTA) scans. However, in some patients with acute ischemic stroke, these veins appear asymmetrical by CTA. The asymmetry is thought to be caused by reduced drainage of one of the veins, resulting from obstructed blood flow in the brain arteries.

In a study published in the January 2014 issue of the *Journal of Stroke and Cerebrovascular Diseases*, Dr Sharma and team retrospectively analysed data from 226 Asian patients with acute anterior circulation ischemic stroke. The purpose of the study was to evaluate the association of various patient factors with the functional outcome 3 months after treatment, assessed using the modified Rankin scale.

Of the factors evaluated, ICV asymmetry (identified by CTA on day 2 after therapy was administered) had the strongest association with functional outcome. Patients with ICV asymmetry were 20 times more likely to have poor functional outcomes after 3 months than were patients without ICV asymmetry (i.e., with symmetrical ICV). ICV asymmetry may be useful as a marker of inadequate blood circulation in the brain and as an early indicator of poor stroke outcome. Larger prospective studies should help to confirm this role.

**Reference**

Host genetic polymorphisms as useful additional factors in risk assignment and treatment selection in paediatric acute lymphoblastic leukemia (ALL)

When selecting the most appropriate therapy for children with ALL, clinicians often use patient risk factors to predict treatment response and assign risk. This personalisation of treatment has in turn contributed to the high cure rates of ALL. However, treatment response still varies considerably among patients. Since this variation cannot be explained completely by known factors such as age and cytogenetics, researchers have evaluated additional host factors for their effect on treatment response.

A recent study by Lu, et al., published in March 2014 in the British Journal of Cancer, indicates that \(ABCB1\) and \(IL15\) gene polymorphisms affect treatment outcome in a group of mostly Asian children aged from 1 to 18 years. The \(ABCB1\) 2677T/T and 3435T/T genotypes were associated with poorer event-free survival (EFS) than other genotypes at these gene loci, especially in patients with favourable cytogenetics. The \(IL15\) 67276493G/G genotype was associated with poorer EFS and lower overall survival than G/C and C/C genotypes, especially in patients lacking common chromosome abnormalities.

Interestingly, the 1 high-risk \(IL15\) and 2 high-risk \(ABCB1\) polymorphisms had an additive effect on EFS and relapse risk, regardless of cytogenetic findings. \(ABCB1\) polymorphisms are thought to influence the response to dexamethasone, the chemotherapy drug used in the study, by affecting intracellular levels of the drug. \(IL15\) polymorphisms affect cell-mediated immunity, which in turn influences the minimal residual disease (MRD) remaining after initial therapy, an indication of treatment effectiveness.

These findings suggest that \(ABCB1\) and \(IL15\) polymorphisms could help supplement existing factors in the risk stratification and treatment selection for ALL in Asian children. Studies in additional patient populations are needed to determine whether the polymorphisms affect treatment response in other ethnicities.

Reference

Lu Y, Kham SKY, Ariffin H, Oei AMI, Lin HP, Tan AM, Quah TC, et al. (last author AEJ Yeoh) Host genetic variants of \(ABCB1\) and \(IL15\) influence treatment outcome in paediatric acute lymphoblastic leukaemia. Br J Cancer. 2014;110:1673-1680.

New Faculty Feature -
Introducing: Associate Professor Matthew Wook Chang

Associate Professor Matthew Wook Chang, who joined the Department of Biochemistry at the NUS Yong Loo Lin School of Medicine in November 2013, is no stranger to communicating his research to the public. Apart from scientific articles, his work in the field of synthetic biology has been featured more than 100 times in such popular media outlets as Discover magazine, The Economist, and The Telegraph.

As A/Prof Chang sees it, synthetic biology focuses on applying standardisation practices from engineering to the systematic design of biological systems that have functions that do not exist in nature.
A/Prof Chang’s own research involves engineering bacteria and yeast cells for biochemical production and therapeutic applications. For example, his team has engineered yeast cells that require two input signals for protein production. This allows production to be turned on only when cell conditions are optimal. Afterwards, production is regulated in real-time based on the concentration of a key intermediate. These mechanisms fine-tune the cell to conserve cellular resources, thus increasing the efficiency of protein production.

Another important aspect of biochemical production in cells is the viability of the cell factories themselves. A/Prof Chang’s lab is studying how to increase cell viability by limiting the toxicity of certain products, engineering global transcription factors to increase the cells’ stress tolerance, producing better biocatalysts, and balancing the levels of cofactors in biocatalytic pathways. For example, the Chang lab has designed yeast cells that continuously produce hydrocarbon alkanes, which are useful as biofuels but toxic to cells. As the alkanes are produced, they are pumped out via transporters engineered on the cell surface. The beauty of this system is that it preserves the viability of the alkane factory (the yeast cell) while providing a convenient means of harvesting the product.

On the therapeutic front, A/Prof Chang’s team has engineered *E. coli* that sense *Pseudomonas aeruginosa* bacterial pathogens, move towards them, and kill them using a “double whammy” approach: 1) breaking up the bacteria biofilm with DNase I, and 2) killing the bacteria with the antimicrobial peptide microcin S. The team is currently testing these targeted *E. coli* killers in animals; if results are promising, the plan is to eventually test them in humans as an alternative to antibiotics. This treatment could be especially beneficial in people with multidrug-resistant *P. aeruginosa* infections.

Going forward, A/Prof Chang is planning to use synthetic biology systems to produce therapies for other diseases such as metabolic disorders. Given the fact that synthetic biology is a new field, much of the research remains at the proof-of-principle stage. Although several applications are currently being tested in animals, clinical studies are still relatively scarce. A/Prof Chang is optimistic that his move to the Medical School will facilitate collaborations with clinicians to develop more therapeutic applications using synthetic biology, test these new therapies in clinical trials, and eventually make some of them available to patients.

**References**

News from RO:
To: Investigators submitting DSRB applications, and Department Representatives endorsing DSRB applications

This is a gentle reminder that PIs should provide sufficient lead time (at least 4 working days) for both Department Representative (DR) and Institutional Representative (IR) to endorse the application. For review of full board studies, submission deadline stipulated by DSRB is the 1st working day of each calendar month. If DSRB receives the study by this deadline, it will be reviewed within the same calendar month.

To allow both DR and IR sufficient time to review/query/endorse the application, please submit the application at least 4 working days prior to the 1st working day of the month. Submissions received after this deadline will be tabled for the subsequent full board meeting. For more information, please click HERE.

For feedback/comments on the NUHS Research Bulletin: email nuhs_research_office@nuhs.edu.sg

About the National University Health System (NUHS)

The National University Health System (NUHS) groups the National University Hospital (NUH), the NUS Yong Loo Lin School of Medicine, the NUS Faculty of Dentistry and the NUS Saw Swee Hock School of Public Health under a common governance structure to create synergies for the advancement of health by integrating clinical care, research and education.