Biomechanics at Macro to Nano-scale Levels

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Invited Paper

ABSTRACT

Today's biomechanics research is not quite the same as what it was decades ago. While institutes around the globe has embarked on the same journey of discovering 'new biomechanics', the biomechanics research advancement in the Southeast Asian region has grown similarly and has strengthened considerably the core skills from the macro-scale level right down to the nano-scale level. Over the years, we have developed expertise, specifically in the employment of nano-technology to understand cellular and molecular biomechanics in pathology, and in the integration of computational modeling and in-vivo experimentations to address issues in bone remodeling, injury risk prediction, prosthetics design and artificial muscle development. This article reviews several important research developments in the field of biomechanics from macro-scale to nano-scale level, particularly through our viewpoint.

Keywords: Biomechanics; Prosthetics; Mechanotransduction; Post-traumatic knee injuries; Nano-biomechanics

1. INTRODUCTION

Biomechanics research worldwide, especially in Southeast Asia, has progressed significantly over the past decades. From studies of gait analysis, and prosthetics and orthotics research in the early days, the region has now taken a huge step forward into integrating biomechanics research with nano-technology, computational modeling and life sciences, giving birth to potential applications specific to cellular, molecular, injury and computational biomechanics. Despite the dominant support for other bioengineering fields such as tissue engineering and bioimaging, the regional biomechanics research has been constantly reinventing and shifting its focus towards a more multidisciplinary approach. Armed with this approach, we aim to

establish our own niche within the international bioengineering community and to develop useful applications that will benefit healthcare, in terms of rehabilitation, injury prevention and drug development. This paper highlights some of the key advancements in biomechanics research from macro-scale to nano-scale level based on development at the National University of Singapore.

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2. RESEARCH AT THE MACRO-SCALE LEVEL

2.1 Biomechanics in prosthetics

Prosthetics research has been a major player in the field of biomechanics, especially at the macro-scale level. Most prosthetics-related issues dwelled heavily on the stump-socket interface pressure, which is a protagonistic factor that can affect the gait and comfort of the amputee donning the prosthesis. Hence, understanding the stump-socket interface pressure would present a valuable aid to socket design in prostheses. One prominent study by Lee et al.(1997)[12] investigated the stump-socket interface pressure distribution, based on a strain-gauged type load cell, in the quadrilateral and ischial containment type sockets. This study fitted two volunteer trans-femoral amputees with both types of socket and measured the interface pressure distributions during standing and walking tasks. Peak interface pressures of 34 kPa and 95 kPa were obtained for standing and walking respectively; higher pressures were found at the proximal brim of the quadrilateral socket while the ischial containment socket exhibited a more evenly distributed pressure profile. Though the interface pressure distributions on the medial and lateral walls of both types of socket were similar, substantial differences were observed in the anterior and posterior walls. The pressures recorded at 10% and 50% gait cycle at the medial and lateral socket walls are consistent with the pressure distribution predicted by [17].

While this former study discussed a system to measure stump-socket interface pressure in trans-femoral amputees, we have also established a similar methodology to evaluate the pressure distribution at the stump-socket interface in trans-tibial amputees wearing the patellar-tendon-bearing (PTB) socket [7]. Briefly, a specially-built strain-gauged type pressure transducer was employed to assess the interface pressure distribution in four unilateral trans-tibial amputees; pressure and gait parameters were measured simultaneously while they executed standing and walking tasks. Based on the pressure profiles compiled at 10%, 25% and 50% gait cycle, the anterior-posterior pressure profiles of the subjects were var-

ied. Additionally, the subjects displayed an elevated pressure at the patellar tendon region during toe-off. Generally, their mediolateral pressure profiles were fairly similar, wherein high pressure was noted at the medial proximal and lateral distal regions. Though the subjects' pressure profiles did not bear resemblance to previously predicted pressure profiles [16], we expect the discrepancy to be attributed to the notion that the resultant pressure profiles are not influenced solely by the ground reaction force.

We then sought to evaluate the stump-socket interface pressure in amputees wearing a socket fabricated by a pressure casting system [8]; this socket produces equally distributed pressure at the stump/socket interface, deviating from the conventional perception that pressure varies in proportion to the pain threshold of different tissues in the stump. In this study, we instructed five unilateral trans-tibial amputees to wear a pressure cast socket and walk at a self-selected speed. The socket was fabricated while the subject placed his stump in a pressure chamber and adopted a normal standing position. Based on our pressure distribution measurements, the pressure cast technique was able to provide comfortable fitting sockets, though a hydrostatic pressure profile was not evident during standing or gait. Our results also indicated that no standard pressure profile for the pressure cast socket was observed; this was expected as no rectifications were done on the pressure cast socket. This study clearly illustrated that the hydrostatic theory is an appealing concept in socket design as it produces an evenly distributed stump-socket interface pressure profile. Furthermore, it is a method that is easily implemented with low manufacturing time and is independent of a prosthetist's skill.

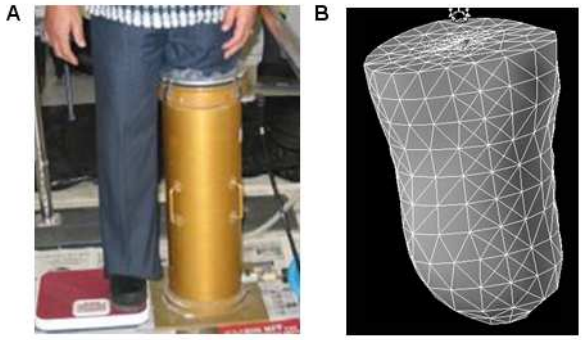

Fig.1: *(A) Subject with stump in DPcast tank (B) FE modeling of patient's stump-socket interface*

Branching from these interface pressure studies, we have then delivered a new hydrostatic pressure-casting technique which facilitates fabrication of a direct-pressure cast (DPcast) socket out of braided carbon fibre in two hours (Fig. 1A) [6]. This research has progressed towards enhancing its application through a combination of in-vivo experiments and FE modeling (Fig. 1B). The traditional artisan method of casting or fabrication of the prosthetic socket is labor-intensive and time-consuming with little or no repeatability in remaking the same socket should the amputee requires it. We have also merged FE analysis (FEA) and rapid manufacturing to fabricate a definitive and first-fitting socket within hours [4-6]. Currently, an in-house program was effectively developed to automatically mesh the computer-aided design (CAD) models into FE models. An in-house-built RM machine fabricates the sockets which undergo ISO 10328 standards testing. The interface pressure measured from the experiments correlates well with the predicted pressure distribution from the FEA gait cycle. In addition, similar functional characteristics (average difference of 5%) between the RM socket and traditional socket were observed.

The incorporation of CAD and computer-aided manufacturing into prosthetic application is justified by the reality that it is able to simplify the socket rectification process and improve reproducibility without introducing any new principle into socket design. Integrating FE analysis to CAD further provides a more objective assessment of socket fit and improve the chance of a successful first fitting. Therefore, we investigated the feasibility of establishing a FE model generation technique directly from geometrical information via a commercial prosthetic CAD workstation [5]. Our in-house program automatically performs meshing of the stump geometry and assigns suitable material properties, load and boundary conditions to the model. The model was validated by comparing predicted pressure with experimentally measured values for one amputee subject. Our findings demonstrated that the predicted pressure distribution has a root-mean-square error of 8.8 kPa compared to experimental values at 10%, 25% and 50% of the gait cycle. Our method was able to develop a FE model to predict interface pressure reasonably well and can be integrated with prosthetic CAD system to provide quantitative feedback to the prosthetist in an automated process.

2.2 Biomechanics of artificial muscles

While we have devoted a majority of our efforts towards prosthetics research, we have also invested into emerging fields such as artificial muscles. As biological muscles are optimized systems that can provide complex and efficient actuation, it inspired the research and development of artificial muscles in the form of electroactive polymers (EAP) by offering as a more efficient, lighter, cheaper, smaller alternative actuation with wide possible applications. Our laboratories are in the process of identifying and characterizing possible EAPs that can match the muscles in the human upper limb. We are also looking into the synthesis of EAPs through specialized experimental techniques and the development of a platform to

quantify their actuation capability.

A recent review [3] depicted a series of latest EAP materials, such as ionic polymer-metal composites, that have emerged and are able to produce a substantial change in shape or size in response to electrical stimulation. These materials have appropriate functional similarities to biological muscles, hence enabling the development of novel capabilities that were previously impossible to achieve. A variety of innovative devices and mechanisms, such as robotic arms, miniature grippers and catheter steering elements, have been demonstrated. Therefore, in terms of prospective medical devices and artificial muscle prostheses, these materials offer abundant advantages for their flexibility, controllability and fracture toughness, together with low mass and power requirements.

3. RESEARCH AT THE MICRO-SCALE LEVEL

3.1 Bone biomechanics

The focus of bone biomechanics is attuned towards bone remodeling and instability analysis, particularly in tumor bone. Cancer-induced bone remodeling was introduced in rats to assess its effect on bone structural properties with time. These structural changes (axial, bending and torsional rigidities) are measured non-invasively using micro-computed tomography (micro-CT). It is likely that as tumor growth perpetuates, the measured structural properties and predicted fracture load of the involved bone diminishes.

One previous relevant study by [10] investigated the application of micro-CT for the assessment of density differences and deterioration of three-dimensional architecture of trabecular bone in an experimental rat model for tumor-induced osteolytic defects after 28 days post-induction. Their results showed a significant reduction in density and architecture parameters in tumor-bearing bones compared with the contralateral control group. This study suggests that the employment of a non-destructive method like micro-CT is mandatory so as to reliably quantify the structural changes of the affected bones.

Another pertinent study sought to understand how the normal aging process can render the proximal femur to be structurally unstable, making certain sites vulnerable to fractures. This work entails the development of a deformable, realistic 3-D model of the proximal femur to illustrate that certain femoral cross-sections become structurally unstable under unaccustomed loads despite adaptive processes that keep maximum stresses within normal limits for physiological loads. Furthermore, a recent report has demonstrated that serial trans-axial quantitative computed tomography (QCT) scans, coupled with engineering beam structural analysis, through human femora with simulated lytic defects at the proximal femur is able to predict the failure load and the fracture site better than current clinical guidelines [11]; this implies that QCT-measured structural rigidity is beneficial in assessing the load-carrying capacity of femurs with metastatic defects and structurally-weakened tumor bones.

3.2 Bone mechanotransduction

Our bone-related studies have also recently evolved towards mechanotransduction; mechanical loading regulates physiological processes at molecular, cellular or systemic level to maintain bone remodeling homeostasis by modulating bone formation or resorption. Computational models of cellular dynamics, based on systems biology, are currently developed to address the role of intracellular signaling network of the bone upon activation from mechanical stress. Integrative systems modeling using control theory is also used to predict network sensitivity and adaptive responses in simulated cells. Additionally, network disruption is further introduced to simulate elevated bone resorption and diminished bone formation, which are important hallmarks of osteoporosis.

This aspect can be exemplified in part by a relevant study [18], in which the authors developed a computational model, coupling bone-cell metabolic expressions to the local mechanical effects of external bone loading. They assumed that the osteocytes within the bone tissue organize the recruitment of bone-forming osteoblasts and bone-resorbing osteoclasts, by sending strain-energy-density (SED)-related signals to trabecular surfaces through the osteocytic canalicular network. Based on their comparisons of the effects of the local loading variables (SED, maximal principal strain and volumetric strain) to their spatial gradients on the morphological predictions of the computational model, they notably found that all these variables produced reasonable trabecular structures. Their model serves as a suitable tool to investigate relationships between mechanical forces, its metabolic effects and bone architecture; moreover, their results strongly suggest that coupling of osteoclast resorption to osteoblast bone formation through the effects of stress concentrations around resorption lacunae can be safely assumed.

3.3 Biomechanics of post-traumatic knee injuries

For injury biomechanics, major efforts have been directed towards investigating the effect of a landing impact on the outcome of post-traumatic knee injuries, especially the anterior cruciate ligament (ACL) tear and tibiofemoral (TF) cartilage damage. Essentially, this research branches into 4 main stages: 1) understanding the knee joint kinematics and forces during landing tasks performed by live subjects, 2) development of an impact test protocol for human cadaveric specimens to simulate landing and, as well

as, induce ACL and TF cartilage injury, 3) construction of a dynamic knee finite element model to predict impact stresses and injury thresholds of these soft tissues and 4) development of appropriate design criterions for knee protection devices to reduce injury risk during impact.

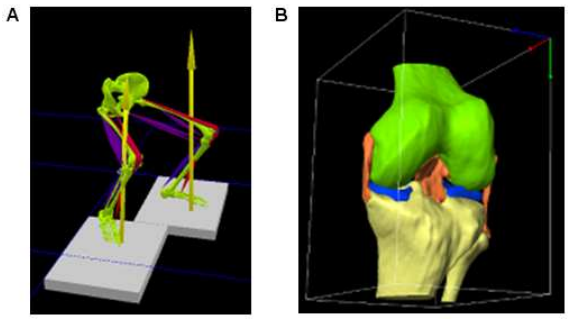

Fig.2: *(A) 3D musculoskeletal model of the lower body. Kinematics of the lower limbs and the corresponding ground reaction forces, which were obtained from landing trials performed by live subjects, were inputted into the model to predict muscle forces during landing. (B) FE modeling of a tibiofemoral joint. Knee joint geometry (tibia, femur, patella and fibula bone segments) and soft tissue structures (articular cartilage, menisci and ligaments) were segmented and reconstructed from magnetic resonance images of an intact cadaveric knee specimen.*

Our preliminary findings from landing studies on live subjects indicate strong positive correlations of the ground reaction forces and external knee flexion moments with landing height. Kinematics of the lower limbs and the corresponding ground reaction forces were subsequently obtained from the landing studies and inputted into a 3D musculoskeletal model of the lower body to predict muscle forces during landing (Fig. 2A). Based on the subjects' landing kinematics, we have successfully developed a standardized test protocol for simulating impact landing and inducing ACL and TF cartilage injury in whole porcine [23] and human cadaveric knee specimens. Our histological results indicate that the extent and distribution of cartilage lesions at the microscale level are indicatory of the ACL failure mechanism; the presence of post-traumatic cartilage defects following ACL failure may heighten the risk of developing early-onset osteoarthritis [23]. In order to acquire the ACL load during an injurious impact, we are in the pipeline of developing a tibiofemoral joint FE model to facilitate us in predicting the force that can result in ACL failure (Fig. 2B). Nevertheless, our understanding of the ACL failure mechanism based on this impact protocol has further enabled a quantitative evaluation for the design criterions necessary to ensure the injury prevention efficacy of knee protection devices.

Furthermore, cartilage lesions can be directly inflicted by excessively large contact stresses (>25 MPa) in the knee joint during activities that involve deep flexion; these damages may be the precursor to the development of degenerative disease of the joint. Thus, we have also previously examined and applied the forces in the knee joint, derived from previous studies on human walking and squatting, to five cadaver knees that underwent quasistatic mechanical testing [16]. This was conducted using a material-testing machine and a custom-made apparatus that allowed secure and consistent loading of the knee specimen in flexion beyond 120 degrees. A thin-film electronic pressure transducer was inserted into the cadaver tibiofemoral joint space to measure contact stress distribution. Our results suggested that contact stresses peaked to 14 MPa during various knee postures simulating specific phases of walking. In deep flexion, the peak stresses were significantly larger by over 80%, reaching the damage limits of cartilage. The significance of this study is that the articular cartilage may not be adequate to support loads in the knee joint during deep flexion.

Due to this particular insufficiency of the articular cartilage, we then sought to investigate the mechanical properties and morphological characteristics of articular cartilage at different regions on the tibial plateau [16]. We utilized a 1-mm diameter flat-ended cylindrical probe to apply a constant load (0.6 MPa) at specific sites on the tibial plateau; the mechanical properties of articular cartilage were determined for seven cadaver knees. Histological sections of the articular cartilage were also performed to study microscale level differences between menisci-covered and exposed cartilage regions. Compared to exposed cartilage regions, the menisci-covered cartilage exhibited a considerably larger modulus by as much as 70%, and was less thick by 40%. Additionally, the subchondral bone quantity and calcified layer thickness were found to be significantly diminished in the menisci-covered cartilage regions. Based on our findings, we have uncovered a significant difference between the mechanical properties and associated structures of articular cartilage in the exposed and meniscicovered regions. This further suggests that the exposed cartilage region is more primed for load-bearing than its neighboring menisci-covered cartilage regions.

We subsequently studied the effect of impact loading on various regions of human tibia plateaus (with menisci removed) via a drop test using a 5-mm indenter [21]. Osteochondral blocks containing the failure site were then extracted, chemically fixed, dehydrated, gold-particle coated, and sent for X-ray micro-CT imaging to obtain 3-D image reconstructions of the cartilage and underlying bone. Post-impact cartilage failure seemed to be characteristically brittle in nature; impacted cartilage from the exposed region exhibited a relatively large cavernous

disruption with microcrack propagation extending radially into the subchondral bone, while impacted cartilage from menisci-covered regions showed less dramatic surface disruption and with no underlying bone failure. This study implies two possible different failure mechanisms in which osteocartilage at different regions of the tibial plateau respond to an indentor impact force.

Altogether, these studies have indicated our recent progress in micro-scale level biomechanics research. Much of our focus was allocated towards understanding bone tumors and defects, and post-traumatic knee injuries such as ACL injury and cartilage damage; we have accomplished these studies via a combination of conventional techniques, such as general histology, and advanced instrumentation like MRI, QCT and micro-CT. While micro-scale level research is not new, there are still many questions to be resolved at this level in the field of biomechanics.

4. RESEARCH AT THE NANO-SCALE LEVEL

4.1 Biomechanics of diseased cells

A plethora of nano-technological techniques have been recently developed and employed to investigate single cell and molecular biomechanics. Research at the nano-scale level involves the use of highly sophisticated instrumentation, such as the laser 'tweezers' which has been used to stretch red blood cells to study the stiffness of Malaria-infected cells (Fig. 3A) [13] while microfluidic channels have been developed to examine the clogging mechanism of these 'stiff and sticky' infected cells flowing through blood vessels and capillaries. Furthermore, atomic force microscopy (AFM) was used to determine how the intracellular and molecular structures within the cells change with the advancing stages of infection (Fig 3B).

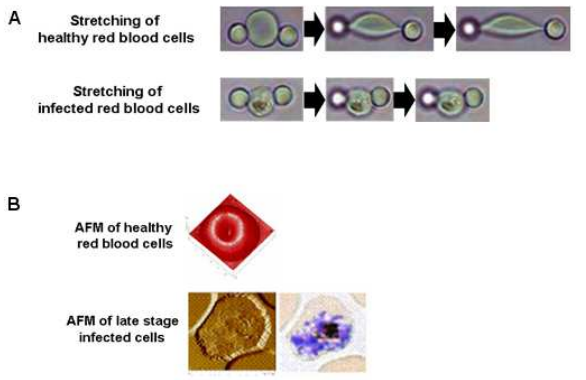

Fig.3: *(A) Stretching of healthy and infected red blood cells using laser 'tweezers'. (B) AFM imaging of healthy and infected red blood cells.*

In fact, earlier studies by other research groups have evidently demonstrated the capability of the AFM in characterizing the malaria-infected red blood cells. A relevant study by [1-2] made use of AFM to study the structure of the knobs of unfixed Plasmodium falciparum-infected red blood cells; each knob was noted to consist of two distinct subunits, which were never observed in chemically fixed knobs examined by conventional transmission electron microscopy. Infected red blood cells adhere to endothelial cells via these knobs that were induced on the red blood cell membrane by the malaria parasites. Hence, they propose that the subunit structure of the knobs may be a steric necessity to align adherence molecules in order to exert a cyto-adherence effect wards endothelial cells; this study concludes that the AFM has great potential for examination of cells in their native state. And in the aspect of improving the use of AFM for biological applications, Nagao et al. (2000)[14] subsequently described the first cellular application of carbon nanotube (CN) probes for AFM studies to obtain topographic and phase images of Plasmodium falciparum malaria-infected red blood cells. They illustrated that that the CN probes are able to generate markedly high lateral resolution profiles than previously-used tapping-mode etched silicon probes and are beneficial for future cellular AFM studies. Clearly, this research has paved the way towards a better understanding of the disease; this will aid us in developing therapeutic strategies to interfere with these changes and perhaps reduce the disease's virulence.

4.2 Biomechanics in tight junction molecules

Alterations in structural and adhesion properties of tight junction proteins underlie several diseases like asthma and cancer. Techniques, such as the AFM and the dual micropipette assay, allow a quantitative measurement of cell-cell adhesion strength (Fig. 4A). One previous study illustrated that the use of single molecule force spectroscopy permitted the determination of the kinetic properties and adhesion strength of homophilic claudin-1 interactions. The results revealed weak and short-lived interactions between claudin-1 molecules which render them highly unstable and dynamic; this is in line with the concept wherein breaking and resealing of tight junction strands regulate the paracellular solute diffusion (Lim et al., 2007).

We have also conducted a similar study on nectins, which are Ca^{2+}-independent cell adhesion molecules localized at the cadherin-based adherens junctions [22]. AFM was employed to examine the interaction of a chimera of extracellular fragment of nectin-1 and Fc of human IgG with wild-type fibroblasts that express endogenous nectin-1; we also aimed to clarify the biophysical characteristics of homophilic nectin-1 trans-interactions at the single molecular level. Our bond strength distribution results revealed three dis-

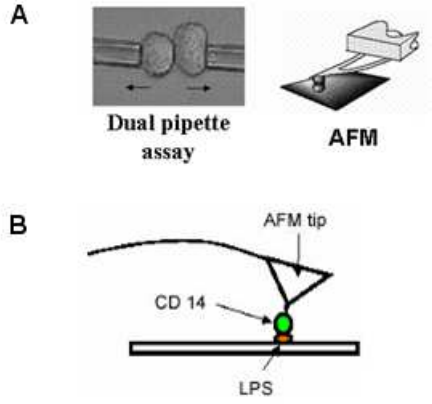

Fig.4: *A) Quantifying cell-cell adhesion using dual pipette assay and AFM. (B) Studying CD14-LPS molecular interaction using AFM.*

tinct bound configurations of trans-interactions between paired nectins, where each bound state has a distinct unstressed off-rate and reactive compliance. Furthermore, kinetic analyses indicated that the force-dependent off-rate of the bound state involving trans-interacting V-V domains between paired nectin-1 was very similar to that of E-cadherin, implying that V-V domain trans-interactions may be essential to initiate and promote adhesions of E-cadherin at adherens junctions. Altogether, these biomechanistic studies can contribute greatly towards a more efficient delivery of drugs that may otherwise be poorly transported across cell membranes.

4.3 Molecular biomechanics for drug development applications

In addition, it is widely-known that high levels of lipopolysaccharide (LPS) can induce septic shock through activation of inflammation from CD14 receptor binding. Therefore, force spectroscopy using the AFM has been recently utilized to study the intermolecular interactions in terms of the forces required to break a CD14-LPS bond (Fig. 4B). The force was measured from force-distance cycles obtained from using force spectroscopy under various loading rates. This methodology can be used similarly to map the unbinding energy landscapes of developing drugs/molecules with LPS. This technique is promising as it can facilitate evaluation of the effectiveness of drugs developed with the aim of inhibiting CD14-LPS binding. One similar study was performed by Kim et al. (2007), whereby they utilized AFM to show that the antimicrobial peptide, polymyxin B (PMB), affects the molecular interaction between LPS and immune proteins (lipopolysaccharide binding protein [LBP] and CD14). They immobilized LBP and LPS onto the AFM tip using a chemical spacer linker so as to simulate an in-vivo interaction. The interaction between the proteins on the tip and model lipid bilayer biomembranes including CD14 was then examined in the presence and absence of PMB. Interestingly, their results noted that in the presence of LPS, the binding force between the LBP-LPS complex and CD14 was considerably elevated, compared to the condition where LPS is absent. Hence, they speculated that LPS may have a vital control on the binding of LBP to CD14, and the antimicrobial peptide PMB is able to specifically inhibit the binding between LBP-LPS and CD14 beyond a particular concentration threshold.

While the nano-scale level research is still largely a mystery, the recent intriguing studies that were performed based on nano-technology instrumentation strongly elucidated the almost limitless potential of biomechanics research at the cellular and molecular levels.

5. CONCLUSION

The noteworthy advance in the regional biomechanics research can be attributed to the culmination of research expertise and efforts from both regional and foreign talents at the National University of Singapore. Over the decades, we have acquired the technological capabilities to investigate biomechanics from macro-scale to nano-scale levels, and to explore the realm of biological molecules, cells, bones, cartilage, ligaments, artificial muscles, prosthetics, pathology and simulation models. Collectively, this new knowledge will bring us closer to our goal of developing potential treatments and applications for a wide range of clinical problems.

6. ACKNOWLEDGMENT

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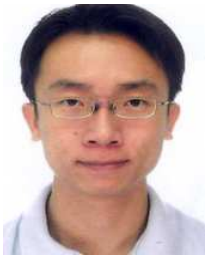

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