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ACCELERATING **RESEARCH & INNOVATION**

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Special Feature: Innovation & Research Corridor 2022

NHG-LKCMedicine Joint Research Symposium in Aug 2022 on Metabolic Health

View more »

Celebrating Our First NHG Clinician Graduates of the LKCMedicine PhD by Research Programme

View more »

Congratulations to Dr Bryan Tan on Receiving the INEX-OSCAR Award 2022

View more »

LATEST NEWS

- Uncoding Schizophrenia Through DNA Codes
- NHG Research & Innovation Awards (NRIA) 2022
- Outcomes of the Nov 2021 NMRC Call for Applications

RESEARCH AND INNOVATION

- The Important Role of Biostatistics in Advancing Mental Health Research

CAREER DEVELOPMENT

- NHG Office of Human Research Protection Programme (OHRPP) is Hiring!
- Training Calendar
- Chicken Soup for the Busy Coordinator

NHG-LKCMedicine Joint Research Symposium on Metabolic Health (17 August 2022)

Metabolic Health is one of the niche focus areas of NHG and LKCMedicine. Both organisations are committed to inter-disciplinary translational research in this area to advance knowledge, address unmet clinical needs and achieve better health outcomes for patients.

Jointly organised by NHG and LKCMedicine, the symposium featured a series of talks by exemplary clinicians and scientists who shared insights on topics ranging from the **effect of microbiome on metabolic health, the role of sirtuin 1 in diabetes, underlying causes of obesity in Singapore context, and the use of infrared thermography for Brown Adipose Tissue research.**

Missed the symposium? You can view the Zoom recording here.

Outcomes of the Nov 2021 NMRC Call for Applications

Congratulations to the NHG clinicians who have received the National Medical Research Council (NMRC) Talent Development Awards and Research Grants during the Nov 2021 Call for Applications.

Name of PI/ Designation/ Department	HI	Project Title	Grant/Award
Dr Ng Tat Ming Principal Pharmacist (Specialist) Pharmacy	TTSH	Developing betA-lactam pharmacodynamic taRgets in Gram-nEgative bacTeraemia using Physiologically based pharmacokinetic modelling (TARGET)	Research Training Fellowship (RTF)
Dr Hoon Hui Qing Violet Consultant Cardiology	TTSH	Singapore Biodesign Innovation Fellowship Training Programme	Research Training Fellowship (RTF)
Assoc Prof Rupesh Agrawal Senior Consultant Ophthalmology	TTSH	Developing 'Software as a Medical Device' (SaMD) from 3D vitreous-retinal-choroidal imaging modalities, to enhance the clinical management of uveitis	Clinician Scientist Individual Research Grant (CS-IRG)
Dr Liu Jianlin Research Fellow Research Division	IMH	Clinical relevancy of non-criterion: A traumatic events to mental health and clinical utility of transdiagnostic affective factors in identifying subgroups of trauma-exposed patients with severe mental illness	Open Fund Young Individual Research Grant (OF-YIRG)

Congratulations to Dr Bryan Tan on Receiving the INEX-OSCAR Award 2022!

In August 2022, Dr Bryan Tan (Consultant, Orthopaedic Surgery, WH) received the **INEX-OutStanding CS-in-TrAining Research (OSCAR) Award under the Clinical/Health Population Research Category** from the College of Clinician Scientists, Academy of Medicine, Singapore.

This annual award is established to encourage budding clinician scientists undergoing research training in a formal programme with a local or overseas university, and comprise of 3 different categories - i) Basic/Translational Research; ii) Clinical/Health Population Research; and iii) Digital Health/Clinical Innovation.

Following a gruelling two-stage review process of selecting the top abstracts and an oral presentation before a panel of judges, Dr Tan emerged as one of just three recipients of this prestigious award. He is currently pursuing a PhD with LKCMedicine and is supported by the NHG-LKCMedicine Clinician Scientist Fellowship (CSF) and National Medical Research Council (NMRC) Research Training Fellowship (RTF) for his studies.

For more information about the INEX-OSCAR award, please click here.

Dr Bryan Tan (on left) receiving the INEX-OCSAR Award

First NHG Clinicians Graduate from the LKCMedicine PhD by Research Programme

Dr Barnaby (on left) and Dr Yew at the NTU Convocation for Class of 2022
(Source: LKCMedicine)

Dr Barnaby Young (Head, Singapore Infectious Disease Clinical Research Network, NCID) and Dr Yew Yik Weng (Consultant, NSC) are among the first NHG clinicians to graduate from the Lee Kong Chian School of Medicine (LKCMedicine) PhD by Research Programme. Launched in January 2016, the programme admits professionals from various backgrounds and aims to equip them with essential skills to conduct cutting-edge research across domains, including Lifespan Medicine, Population Medicine, Medical Biology, Medical Engineering, and Medical Education Research. In all, 16 PhD graduates received their Doctoral degrees this year.

Dr Young earned his PhD while helping the nation battle COVID-19. He is part of the COVID-19 Research Workgroup (RWG). Like Dr Young, Dr Yew completed the second half of his PhD during the peak of the COVID-19 pandemic. He was attracted to the PhD programme as he was interested in epidemiology research.

Click here for the full article

Source: First published in Together@NHG (1 September 2022), produced by NHG Group Corporate Communications.

Uncoding Schizophrenia Through DNA Codes

An international team of researchers has recently shown that 287 regions in human DNA contain genes that increase the likelihood of schizophrenia. Along with this discovery, they also demonstrated that genetic risk for schizophrenia is found in genes concentrated in brain neurons instead of other cell or tissue type, and had breakthrough findings with the identification of two specific genes associated with rare disruptive coding variants in people with the disorder. With that, they are now one step closer to understanding the biological role of neurons in determining the risk of schizophrenia. Click HERE for the article 'Mapping genomic loci implicates genes and synaptic biology in schizophrenia' published in *Nature* which outlines the key findings.

NHG Clinician Scientist Development Office (CSDO) spoke to **Dr Jimmy Lee** (Senior Consultant, Department of Psychosis and Research Division, IMH and Associate Professor, LKCMedicine, NTU) and **Dr Max Lam** (Principal Investigator, IMH) on their experience being part of this international collaboration and how the findings may impact treatments for the disorder in Singapore.

CSDO: It must have been exciting to be part of the international collaboration! Could you share about your experience and how you became part of the research team?

Jimmy: It started when research into the genetics of schizophrenia had just begun. Quickly, multiple groups around the world started their own studies. But soon, **it became apparent that each individual study would not be adequate to derive meaningful insights. A few leading researchers in the field then proposed to pool resources together to form a research consortium**, culminating in its first *Nature* publication with almost 150,000 genomes. At that point, Singapore formed the largest Asian dataset and but presented an ethnic bias amongst the predominantly Caucasian study population. **The consortium members then sought out partners to ensure better ethnic representation. Since then, the dataset has more than doubled**, leading to the recent publication in 2022.

Max: IMH hired me to be part of the Neuroscience Translational Clinical Research program in 2008 during which patient recruitment had just begun. In 2014, we realised that the genetic data we had was not large enough to draw conclusions and I was **sent to London to train with Principal Investigators running the Psychiatric Genomics Consortium (PGC), a global consortium that seeks to consolidate large-scale genetic databases worldwide** to understand the biology underlying psychiatric illnesses.

Expanding PGC's efforts in diverse populations, particularly those of Asian populations, **we then established PGC-Asia, which focused on examining schizophrenia genetics across Asia, and I took on the role of lead analyst**. Over the next several years, we worked with partners across Asia, culminating in the largest Asian schizophrenia genetics publication in *Nature Genetics*, while the PGC worked to consolidate continental research efforts leading to the current *Nature* publication. We are now preparing for v2.0 for the Asian population Schizophrenia Genetics Study.

CSDO: What is the significance of the study findings? How about in the context of the Asian population?

Max: A critical aspect of large-scale genetic studies is to identify novel biological mechanisms and gene targets where new and novel drugs could be developed to mitigate illness. Two-thirds of new FDA approved medication today are supported by genetic evidence. **In psychiatry, drug development has not really progressed in the last 30 years.**

In the realm of psychosis and schizophrenia, medications today are adept at treating certain positive symptoms (e.g. hallucinations and delusions). However, we also know that conditions like schizophrenia carry with them significant disabilities brought about by negative symptoms (e.g. lack of motivation and significantly reduced social interactions), and cognitive deficits. **The current research study offers new insights into biological mechanisms associated with schizophrenia** and this is significant because **now we have a long list of mechanisms that we can examine to see if they might be amenable to treatment by novel pharmaceutical compounds.**

One of the genes that we highlighted belongs to the *glutamate* mechanism, one of the biological mechanisms implicated in cognitive function. Our study in Asian populations show that biological mechanisms for schizophrenia are broadly similar across populations. However, to further investigate if targeting mechanisms like *glutamate* would yield similar effect cross populations, it would require much larger databases.

CSDO: How would deciphering genetic codes potentially lead to new ways of treating schizophrenia?

Jimmy: It gives us very strong clues to the biological processes that were altered in Schizophrenia. With improved understanding, we can **identify potential targets to develop new treatments**. Additionally, these insights might shed light

on illness development trajectories, which could **inform illness onset prevention or detection** to improve clinical outcomes.

Max: It is essential to 'decipher genetic codes' when it comes to mental illnesses as unlike other medical conditions, there is no way to study diseased tissue or order a biopsy to study the brain. It will be unthinkable to request a piece of the brain in a living individual for clinical examination. That leaves researchers with indirect ways to try and figure out how the brain works and especially what might have gone awry in schizophrenia.

One strategy is to **look for genes that are related to biological processes in the brain and compare how their genetic codes might differ in healthy individuals and patients with schizophrenia**. The caveat is that the effect is miniscule and therefore, large-samples are necessary to amplify those effects for research.

CSDO: Any future research plans following the study?

Max: Upon returning to Singapore, I would be **establishing the IMH Neuropsychiatric Genomics Laboratory**, to continue expanding research insights obtained thus far. We would seek to **venture beyond schizophrenia to cognitive function, dementia, and cardio-metabolic diseases**, using AI methodologies to understand the clinical profiles of patients through eMR research. We also plan to **translate some of the research insights into potential new drugs**, and also **establish new genetic biomarkers** that might help us understand our patient segments and needs better. We have built extensive networks with academic and industry partners and will continue to grow the research and development efforts in Singapore.

Dr Jimmy Lee
Senior Consultant, Department of Psychosis and Research Division, IMH and Associate Professor, LKCMedicine, NTU

"The first lesson I learnt was the importance of collaboration. Having a meaningful research collaboration, growing that relationship, is truly important to our individual research journeys and in attaining the eventual goal of better clinical outcomes."

Dr Max Lam
Principal Investigator, IMH

"In the current research climate, no lab is an island and that team science is the way to go. There will be no one scientist who knows it all, and working in a multidisciplinary way would help reap benefits in a more comprehensive manner, ultimately for the patients' benefit. For budding researchers, do start building the networks and collaborations early both locally and internationally."

Dr Jimmy (center), Dr Max (fourth from right) and the Phenomics team that contributed to the study

Innovation and Research Corridor 2022

The Innovation and Research Corridor (IRC) is part of the Singapore Health & Biomedical Congress (SHBC) and showcases some of the exciting new technologies and innovations that researchers and innovators from the National Healthcare Group have developed either on their own, or together with research, academia or industry collaborators. This series of special feature once again shifts the IRC to an online experience and allows e-Catalyst readers to be updated on some of the projects that would have been exhibited as part of the IRC 2022 had the physical platform gone ahead in SHBC 2022.

Pathophysiology of Itch in Atopic Dermatitis and Psoriasis

Problems/Challenges

If someone suffers from an itchy skin condition like atopic dermatitis and psoriasis for a long time, how will nerves in the skin will change? Traditionally, dermatologists use 2-dimensional imaging of nerve endings in skin to measure how dense nerves are, but this can be problematic especially because nerves stretch out into three-dimensional space. To study this question more accurately, the study team uses **3-Dimensional (3D) imaging of nerve endings in skin**. 3D imaging enables more precise and detailed imaging of nerve architecture in normal skin and pathologies than traditional histology which relies on 2-Dimensional (2D) imaging.

Figure 1: Comparison of uncleared skin with cleared skin

How to make light pass through whole tissues?

Traditional histology relies on the use of thin 2D sections because skin is opaque, making it difficult for light to pass through. However, this results in the loss of information as the team can only sample a very thin volume of skin. To circumvent this, they **make skin transparent by applying a chemical to skin (optical clearing), which allows light to pass through, permitting the visualisation of skin in 3D** (Figure 1).

Findings/Solutions

With 3D imaging, the study team can then sample a greater volume of skin and obtain up to 50 to 100x more information than traditional histology, to put together a complete picture of nerves in skin (Figure 2).

The team was interested to study how nerves may change in patients suffering from itchy skin conditions. **Using 3D imaging, they found a general trend of atrophy in these patients with itchy skin conditions in comparison to healthy individuals.** Nerve fibre length per unit volume was substantially reduced in lesional skin of atopic dermatitis (59.56% reduction) and psoriasis (73.98% reduction) patients as compared to healthy skin. The study has demonstrated a 3D visualisation of the skin biopsy and a statistically significant reduction in epidermal nerve networks in atopic dermatitis and psoriasis patients compared to healthy individuals.

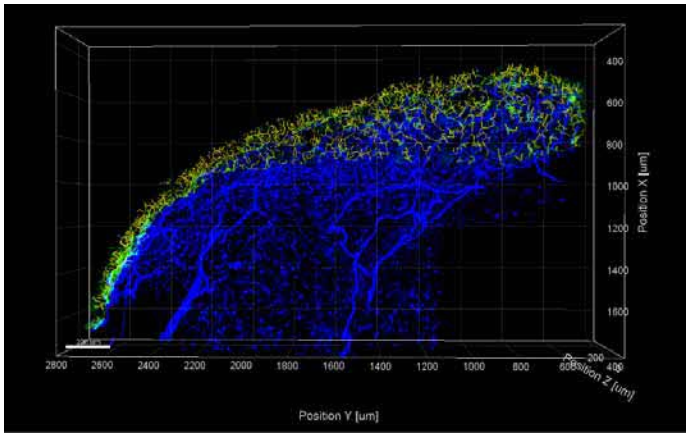

Figure 2: Nerves in a healthy human skin sample

What It Means

3D imaging serves to advance patient care through enhanced understanding of nerve architecture and how it changes in a disease state. This 3D imaging approach has the **potential to enhance therapeutics to treat itch in the future**, such as providing insights to understand the location of known itch-mediating small molecules or cells in relation to the cutaneous nervous system.

Itch, being the most prominent complaint in chronic skin diseases, creates much discomfort, frustration, loss of sleep, anxiety and even depression. **Patients suffering from chronic itch face a significantly lower quality of life** as they may have difficulty sleeping. Their work performance and productivity is also affected from the itching and lack of sleep. **Improving patient management and treatment strategies could thus have significant effects on the patients' quality of life.**

The results of this study have been published in leading dermatological journals, the *Journal of Investigative Dermatology* and *British Journal of Dermatology*.

Future Plans

Following the success in 3D imaging of nerves in skin, the team is currently pursuing the application of 3D tissue imaging in other skin conditions, namely skin cancer. The team will also be looking to expand 3D tissue imaging to other organs in the future.

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Artificial Intelligence-incorporated Automated Adaptable Attachable Dermoscopy for Bedside Algorithmic Diagnosis of Melanoma

Problems/Challenges

(1) Development and validation of Artificial Intelligence (AI) algorithm

Skin cancers are malignant tumours of the basal cells, keratinocytes and melanocytes found in the epidermis. Skin cancers are divided into **melanoma and non-melanoma skin cancer** (NMSC – Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC)). There is a high incidence of skin cancers both locally and worldwide. **Early detection and accurate diagnosis is crucial**, especially for melanomas. This would allow for **prompt treatment, reducing mortalities and morbidities**.

Public and family physicians may not be able to pick up skin lesions that are early cancers. **Dermatologists rely on clinical examination as well as the additional use of a dermoscope**, a handheld device, **to examine the skin structures and patterns**. The study team is working to **develop 2 versions of an AI software to effectively identify skin cancers**, allowing for earlier interventions and better outcomes for patients.

(2) Development of an attachable dermoscope

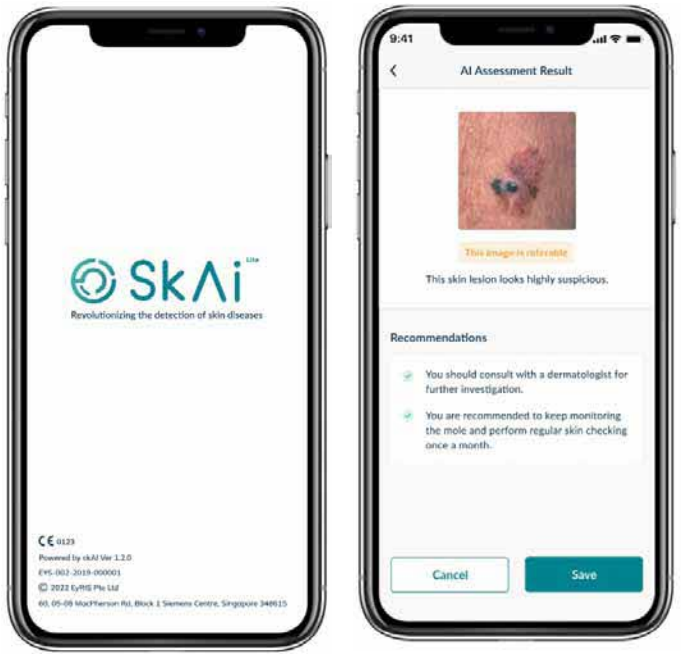
Current available attachable dermoscopes are **expensive, bulky and require an adapter to allow pictures to be taken either via a hand phone or a camera**. This **slows down the process and deters some users from obtaining dermoscopic pictures** in a busy clinic. Most brands of attachable dermoscopes are designed for specific hand phone models or hand phone casings and **may not be interchangeable**. This **limits the widespread use of hand phones to take dermoscopic images** for reference and analysis. The team is working to **develop a universal, affordable and attachable dermoscope**, which will streamline clinical workflows by eliminating the time needed to capture images using an extra device and then transfer the images to a computer.

The team applied and was awarded the NHG Centre for Medical Technologies and Innovations (CMTi) and National Health Innovation Centre Singapore (NHIC) Joint MedTech Grant. Upon the success of the proof-of-concept, the team put up a challenge statement under the Enterprise Singapore Healthcare Open Innovation Challenge (HOIC) to further develop the AI algorithm. This has allowed them to collaborate with EyRIS Pte Ltd who was awarded the HOIC funding.

Findings/Solutions

The study team is in the midst of developing 2 AI algorithms to be incorporated into hand phone applications for ease of use.

SkAI Lite is designed for both public and patient use. Utilising a photo of the skin lesion taken by an ordinary consumer-grade digital camera or smartphone (without dermoscope), the in-built AI algorithm on the hand phone application (SkAI Lite) will determine if the **skin lesion is at high risk for skin malignancies** (melanoma, basal cell carcinoma, squamous cell carcinoma) and recommend early review by a dermatologist. This allows **a simple, fast and accurate method for detection of high risk/ malignant skin lesions.** It also allows the public population and high risk patients a way of self-monitoring skin lesions. This would prompt the public to **seek medical attention earlier when needed**, and also enables family physicians to detect suspicious lesions and prompt for early referrals to specialists.



An interface of the hand phone application

SkAI Pro is designed for use by dermatologists. Utilising a photo of the skin lesion taken by an ordinary consumer-grade digital camera or smartphone, with an attachable dermoscope, the in-built AI algorithm on the hand phone application (SkAI Pro) will determine if the **skin lesion is at high risk for melanoma, and recommend early intervention with skin biopsy**. SkAI Pro allows **rapid analysis of the images** and patients will be able to receive a more confident diagnosis at the first visit with the dermatologist. This allows for **discussions and early interventions**, which **reduces patient and family anxieties and improves patient outcomes**. SkAI Pro would enable dermatologists to make a confident diagnosis regarding skin lesions, **reducing unnecessary biopsies and clinical visits**, leading to a **reduction in overall healthcare costs**. The team is working to improve the current prototype, aiming to achieve a **more convenient-to-use design**.

Current Status/Future Plans

The team is planning for a **prospective study to validate the AI algorithm** as well as to obtain feedback regarding the use of the dermoscope.

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Current prototype of the attachable dermoscope, allowing dermoscopic pictures to be taken via hand phone

Artificial Intelligence for Peripheral Blood Films

Problems/Challenges

The traditional method of reviewing peripheral blood films is by light microscopy, and performed by a laboratory technologist. This is **labour intensive** and can be **subject to human fatigue**. **Films with abnormal features or unclear diagnosis** are then **escalated to a haematologist** for further review.

Findings/Solutions

Blade is an **Artificial Intelligence (AI)-powered software** co-developed by engineers from ASUS Intelligent Cloud Services (AICS) and medical professionals from TTSH and KTPH. Blade is **aimed at automating peripheral blood cell identification in the laboratory setting**, which has the capability to automate blood cell identification and **classification with high accuracy**. This means that technologists will only need to load the blood films into a digital slide scanner. The AI tool will then process and analyse the digitalised films and flag any critical findings such as leukaemia, thus **enabling early clinical interventions**. By assisting laboratory technologists and haematologists with the reporting of peripheral blood films, Blade aims to **accelerate the overall review duration by 50%,** thus translating into **better productivity and faster diagnosis**. Through a collaboration agreement signed with AICS facilitated by the NHG Centre for Medical Technologies and Innovations (CMTi), the team utilised a large dataset of over 337,700 digital images of peripheral blood cells to develop the AI-powered software through deep learning and computer vision, with a white blood cell classification accuracy of 91.4%.

Blade, an AI-powered software that assists medical staff in peripheral blood film analysis

Current Status/Future Plans

Blade is **currently undergoing clinical trial and evaluation** at TTSH, KTPH and other collaborative sites such as Hougang Polyclinic and Mt Alvernia Hospital, with **plans for regulatory approval**. The development team hopes to **expand the use of Blade in the community setting**, with Hougang Polyclinic planned as the first pilot site in the second half of 2022 for telemedicine purposes.

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Creation of an In-house 3D Printing Centre for Clinical and Educational Needs

Problems/Challenges

Lack of affordable patient-matched anatomical models and surgical guides

In the age of personalised medicine, there have been many technological advances made through hardware and software development to tailor medical treatment to individual patient characteristics. Despite this, there are still many surgical approaches and techniques that use a traditional one-size fits-all method for planning and execution.

For example, many **pre-operative plans are based upon radiological imaging that is viewed 2D on a monitor screen**. The preoperative plan then relies on the surgeon's **3D perception of the patient's anatomy which is conceptualised in his mind.** This difficult skill leaves room for uncertainty, guesswork and error especially in the hands of less experienced surgeons.

During consultation with patients, the **2D imaging on a computer screen** can be **very challenging to understand.** This invariably affects the patients' understanding of their medical condition and treatment options, which may discourage the patients' involvement in their treatment and health journey.

Although **current options for customised 3-Dimensional Printing (3DP) solutions exist**, they are often outsourced to local companies, or are manufactured overseas. This makes their use **expensive and also requires a long lead time** - factors that are unappealing to clinicians and patients.

Barriers to the wider adoption of the 3DP within the hospital

In recent years, **clinicians were keen to explore clinical applications of additive manufacturing in medicine and patient care.** However, there were many **barriers to its sustainable adoption such as cost, lack of expertise and inadequate quality control. Furthermore, there was also a lack of awareness of the benefits that 3DP could bring** to their practice and patients.

Problem with the outsourcing model

Currently, **most 3D printing activities are outsourced** and such model has **proven to be cumbersome with long turnaround times and is costly.** There are also **potential cyber security risks involved** when transferring information out of the hospital to the vendor. The outsourcing model also creates a gap in the clinician's understanding of the 3D engineer's capabilities, as well as the 3D engineer's understanding of the clinician's needs. This lack of understanding often leads to frustration in failed prints or the inability to meet clinical needs. Individual clinicians and departments have attempted to develop 3DP devices for clinical use through collaboration with external outsourced vendors, only to find problems with the translation of a clinical

concept to the final product. Oftentimes, there is a **disconnect between clinicians and manufacturing companies,** with neither having the expertise in medical product design. The projects are often on an ad hoc basis that have limited outreach. Furthermore, having multiple points of contacts between various clinicians, departments and manufacturing centres **could result in duplication of efforts and resources,** making the whole process less efficient and unsustainable.

Findings/Solutions

With support from the NHG Centre for Medical Technologies & Innovations (CMTi), the study team created an **on-site point-of-care 3DP centre to provide rapid prototyping and manufacturing capabilities for NHG.** An ecosystem was set up to leverage on the 3DP technology, with the **close proximity to healthcare institutions** and the clinical expertise of clinicians **helping to bring about an uptake of 3DP for clinical applications.**

In 2020, a 3DP multidisciplinary workgroup was formed comprising of multiple surgical and medical disciplines, allied healthcare professionals and ambulatory services. This was recognised as an important first step to bring knowledge and awareness to 3DP, through mutual knowledge exchange and sharing of resources. The workgroup helped to promote the clinical applications of 3DP and fostered greater collaborations across disciplines.

Following approval from the Clinical Board and Senior Management, a steering committee was set up to **oversee the development of a 3DP point-of-care centre in TTSH.** Its alignment with TTSH's strategic innovation programme had resulted in the study team being awarded a Digital Prototyping Budget (DPB) grant to collaborate with Eye-2-Eye Communications, and the centre was officially started in Nov 2021 to support clinical and educational needs. Its **capabilities include printing of anatomical models for preoperative planning, educating patients, students and residents, as well as devices for intraoperative usage.**

This innovative ecosystem **allows patients' scanned images to be extracted for segmentation in a secure manner,** as there is no need for transfer of images outside of the hospital. Having a 3DP centre within the healthcare institution could reduce the turnaround time to as short as 2 days. The location of the centre fostered frequent communication between radiologists, surgeons and 3DP engineers. **This in turn facilitates many opportunities for the creation of new intellectual property (IP).**

Over the course of 1 year, more than 100 anatomical models and surgical guides were created, servicing 15 clinical specialties. These include Orthopaedics, General Surgery, Vascular Surgery, Ear, Nose and Throat (ENT), Urology, Dental, Haematology, Plastic Surgery, Hand Surgery, Speech Therapy, etc.

The benefits of 3DP have been promising and have yielded encouraging results. A case series showing the accuracy and cost effectiveness of a novel surgical guide for shoulder arthroplasty was conducted and successfully published. Surveys showed that the use of 3DP **improved the confidence, understanding and satisfaction of surgeons, students and patients. Patients found the anatomical models beneficial in understanding their medical problem and helped them comprehend the treatment options better,** improving doctor-patient communication. Likewise, **surgeons felt that the anatomical models assisted in their pre-operative planning and patient counselling.** Anecdotally, all surgeons agreed that 3DP was beneficial and they would consider using the 3DP adjuncts in future.

Current Status/Future Plans

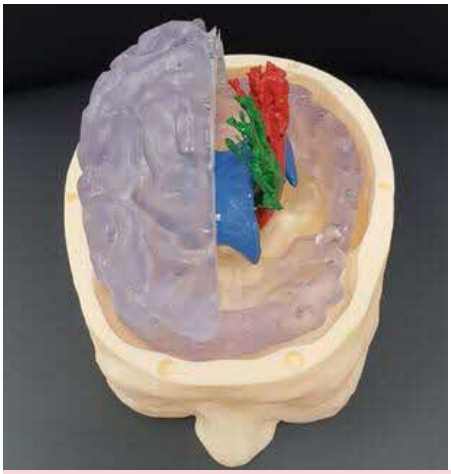
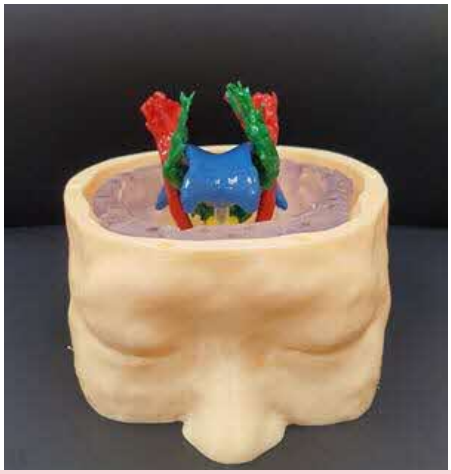
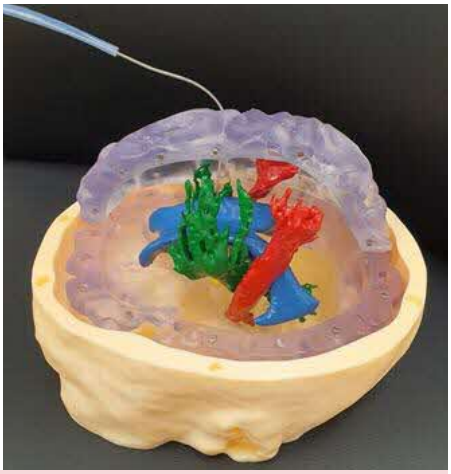
The 3DP centre has plans to eventually scale up operations to meet the needs of the hospital and NHG as a cluster. Early successes had garnered interests from various healthcare institutions, both public and private, as well as academic and industry partners. Many had come to pitch how they might add value to the current centre and to discuss the possibilities of collaboration.

With an in-house center, processes can be streamlined and redundancies removed, resulting in a **reduction of the overall 3DP cost.** The pilot implementation proved to be a sustainable model, with the 3DP service provider being incentivised by the increase in use cases, and clinicians are now able to make use of 3DP more regularly for their clinical needs. This results in a virtuous ecosystem being developed.

The centre looks forward to more multidisciplinary and multi-institutional collaborations with industry partners such as 3DP companies, material providers, medical device manufacturers, and schools such as Nanyang Technological University/Lee Kong Chian School of Medicine to meet future clinical, educational and research needs.

Dr Candice Leong (left) and Dr Michael Yam

Preoperative planning and prebending of metal plates to be used intraoperatively

Anatomical model of the brain with different tracts for patient and student education


Surgical guides for accurate implant placement

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Dr Candice Leong, Radiologist, TTSH Radiology
Mr John Chao, Radiographer, TTSH Radiology
Mr Chen Wen Xiang, Associate, TTSH Radiology

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A Novel Gene Silencer to Lighten Skin Colour

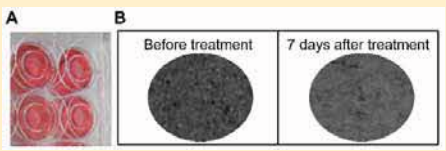
Problems/Challenges

The colour of our skin is regulated by a specific pigment called "melanin". This pigmentary substance is produced by specialised cells present in the skin, known as melanocytes. The more melanin produced by melanocytes, the darker our skin will be**. Excessive melanin production leads to hyperpigmentation disorders, such as melasma, that predominantly affects Asian skin with solar lentigo or sun spots**. Treatment of hyperpigmentary conditions represents a significant healthcare need as **hyperpigmentation can lead to depression and decreased quality of life if untreated**.

Melanin production by melanocytes in the skin is regulated by a key enzyme, called "tyrosinase"; i.e. increased tyrosinase activity in the skin leads to increased melanin production and pigmentation. Several **skin lightening agents** have been developed that **directly inhibit tyrosinase and thus decrease melanin production and exhibit a whitening effect**. These agents include hydroquinone, arbutin, azelaic acid, and kojic acid. **While they are effective, they tend to cause adverse effects.** For example, hydroquinone is linked to DNA damage causing cancer. This drug has been banned in Europe since 2016 and restrictions have been placed on its concentration levels in the USA and Singapore. Over-the-counter creams are restricted to just 2% hydroquinone and a prescription would be required to purchase a maximum of 4% hydroquinone. **Other skin lightening agents cause unwanted side effects.** Recent cases of high levels of mercury in skin whitening products are also a serious concern. Thus, there is a recognised **need to develop a next-generation, safer and effective skin lightening agent.**

Findings/Solutions

With increasing genetic information, it is known that **excessive melanogenesis in hyperpigmented skin is caused by the upregulation of multiple genes, proteins, and enzymes.** This offers the prospective for gene silencing-based therapeutics.



Testing the skin lightening effect of Tyrp1-epAON. A) The reconstituted 3D-skin containing melanocytes was treated with Tyrp1-epAON, single dose for 7 days. B) Images of the 3D-skin before and after treatment showed that the Tyrp1-epAON reduced melanin production and lightened the skin colour.

After studying the melanogenesis pathway and gene regulation, the study team noted that there are many **proteins downstream of tyrosinase that control melanin synthesis**. Therefore, they considered a different approach to target one of the downstream proteins. In the study approach, they targeted the tyrosinase like protein 1 (Tyrp1). The team developed a **chemically modified chimeric "end-protected" antisense oligonucleotide molecule targeting Tyrp1 (Tyrp1-epAON).** They demonstrated that Tyrp1-epAON effectively silenced the Tyrp1 gene with high specificity. Using cultured darkly pigmented melanocytes and reconstituted

3D-skin, the team showed that **Tyrp1-epAON treatment resulted in the cells/3D-skin looking significantly lighter in colour, compared to untreated controls.**

The team further confirmed that **Tyrp1-epAON has acceptable safety profiles with no sign of skin irritation,** as examined in accordance with the regulatory methods of the European Centre for the Validation of Alternative Methods and the Organization for Economic Co-operation and Development (OECD). Tyrp1-epAON is relatively non-cytotoxic to melanocytes as compared to tyrosinase inhibitors, which minimises the possibility of irreversible loss of inherited skin colour i.e. permanent depigmentation.

The Tyrp1-epAON molecules will be useful to treat pigmentary skin disorders such as melasma, with **the aim of improving clinical practice by providing an effective alternative treatment that leads to better health outcomes for patients.** The team strongly believe that the **epAON technology has the potential to be used in the treatment of hyperpigmentary conditions**, which represents the potential market of millions of people worldwide. As a result, they believe there is a clear development opportunity.

Conclusion

There is an increasing need for new treatments for hyperpigmentary conditions. Approximately 15% of the global population spends on skin lightening products. According to a recent report by Grand View Research, Inc., **the global skin lightening products market is expected to reach US$ 16.14 billion by 2030.**

These products have significant demand in Asia. In Singapore, pigmentary disorders are the 4th most common clinical problem encountered at the NSC. Every year in Singapore, the NSC sees about 1,500 melasma cases. **The exceptional innovation of the epAON technology and use of the Tyrp1-epAON molecule would therefore be of interest to dermatology and cosmetic industries.** The study team have developed a novel gene silencer, Tyrp1-epAON, which can be applied topically to effectively silence the Tyrp1 gene and suppress melanin production.

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Designing a Functional, Aesthetically Pleasing and Affordable Footwear for Diabetic Patients

Problems/Challenges

Diabetic patients often have lower limb complications such as **poor blood flow** (peripheral arterial disease) and **poor nerve function** (peripheral neuropathy). In the presence of **reduced pain sensation** in peripheral neuropathy, **poor fitting footwear** can cause **excessive shearing** and **pressure to the feet** without patients being aware.

This may result in **patients sustaining a wound** within the shoe. Patients usually realise only after their shoe is removed at the end of the day or blood is seen on the floor. Patients may **develop an infection** if the wound is left untreated or exposed to dirty environment. This may also increase the risk of amputation depending on the presence of medical conditions or complications.

Patients with foot deformities or healed wounds often **require custom-made insoles to offload, remove pressure and cushion the affected area** in preventing recurrence. However, **available footwear in the market** are often **not designed with a deep and wide toe box that can accommodate the foot deformities or the insoles**. It is also unable to meet the needs of diabetic patients in terms of function (material, structure, function, width and depth of toe box, support, cushioning) and patients often find it challenging in getting an appropriate fitting footwear. The few that can meet the function may be very costly and may not meet the aesthetic demands of patients. This will result in patients not willing to wear the insoles and may lead to detrimental outcomes.

Findings/Solutions

Facilitated by the NHG Centre for Medical Technologies and Innovations (CMTi), the project team is currently in partnership with MBT Distribution Pte Ltd, a global established renowned footwear company that designs and manufactures Swiss engineered and globally patented physiological footwear under the brand name MBT. MBT understood the unmet clinical needs and was interested in the cause of the project to **provide affordable, functional footwear** for the needs of the general population, especially the diabetic population.

Through collaborative discussions and collective feedback from end users, the project team agreed on an **innovative design that incorporates the majority of functions and features** that the team consider appropriate; which is a covered, rocker bottom sole footwear with deep and wide toe box.

The project team is grateful that this project is supported by the Enterprise Singapore as well as the Alexandra Health Fund, and most of all, MBT in sharing their expertise to work on the project with Podiatrists from KTPH. The industry support is instrumental to the success of the project.

Final prototype design with 1 strap

Final prototype design with 2 straps

Current Status/Future Plans

The current design of MBT diabetic footwear will be made **available to patients through KTPH.** The project team **envisions making this footwear available to patients in all public healthcare institutions and developing other trendier models** in the future **to remove the stigma of using a "medical shoe"** for the patients.

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Mr Andy Chaw, Director, MBT Distribution Pte Ltd

Using Magnetic Field Tracking to Confirm Nasogastric Tube Placement at Point of Care, a Feasibility Study

Problems/Challenges

A **nasogastric tube (NGT) is inserted** through the nose into the stomach **to facilitate feeding or decompression in patients with dysphagia or gastrointestinal obstruction**. The need for NGT will likely rise due to ageing, increasing incidence of stroke, dementia and cancers. It is crucial for wrong insertion of NGT to be ruled out before commencement of feeding. There are various methods of confirming NGT placement but each has its limitations [1]. **The gold standard of using chest X-ray (CXR) subjects patients to radiation exposure, is time consuming and labour intensive**. Moreover, CXR is not readily accessible to NGT-dependent patients in the community. **A simple point-of-care-test (POCT)** that confirms the NGT's position in the stomach **can lead to greater cost savings, punctual feeding, and convenience to patients, nurses and caregivers.**

The study team previously faced challenges in looking for suitable industry and academia partners to collaborate with. Through the NHG Centre for Medical Technologies and Innovations (CMTi), they were connected to Prof Louis Phee of Nanyang Technological University (NTU) and his team. Together with Prof Phee, the team **developed a 2-sensor magnetic field tracking system as a POCT for NGT localisation and preclinically validated its accuracy** [2]. This study is the device's first-in-man trial with the aim to determine the feasibility of the prototype in 12 patients.

Findings/Solutions

The clinical trial to determine feasibility of the co-developed solution began in May 2022. 9 patients have been recruited so far. In each patient, they inserted a Neodymium magnet attached to a hydrophilic guidewire into the lumen of the patient's NGT (Figure 1), and placed 2 pairs of sensors housed in a T-shaped frame on their sternum (Figure 2) to track the magnet's trajectory as it was inserted and withdrawn. Thus far, the team has **observed successful tracking in some participants** (Figure 3) and there has been no adverse event. Findings from the clinical trial has value-added to the team's knowledge of how tracking accuracy might be affected and in whom they can apply this device effectively.

Current Status/Future Plans

Since 2020, the team has also received generous guidance and help from various other sources such as TTSH Clinical Research and Innovation Office (CRIO), TTSH research co-ordinators, Clinical Research Unit (CRU) of WH (as this is a collaborative project between WH and TTSH), and Mr Liu and Dr Miyasaka of Prof Phee's laboratory. Through these joint efforts, the team was successfully awarded the NHG CMTi MedTech Grant 2021 to support this trial. The team plans to recruit 3 more patients and aims to complete the clinical trial in the coming months and obtain further funding to refine this device for clinical application.

Figure 1: Each patient was inserted with a magnetic tipped guidewire, within the lumen of the NGT

Figure 2: Placement of the sensors

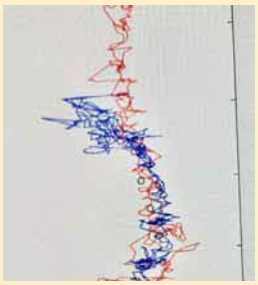

Figure 3: Location of the nasogastric tube as determined by magnetic tracking versus the ground truth from chest X-ray. Red and blue lines: raw data showing the location of the nasogastric tube as determined by magnetic tracking. Black circles: location of the nasogastric tube on chest X-ray

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References:
1. Nasogastric tube confirmation: where we are and where we should be heading. Fan et al. (2017). Proceedings of Singapore Healthcare, 26(3), 189-195
2. Miyasaka M, Li H, Tay KV, Phee SJ. A Low-Cost, Point-of-Care Test for Confirmation of Nasogastric Tube Placement via Magnetic Field Tracking. *Sensors.* 2021; 21(13):4491. https://doi.org/10.3390/s21134491

SMARTVacc: An Automated Vaccine Management System

Background

Polyclinics have a traditional and manual method of storing, picking, ensuring accountability and maintaining the vaccine cold chain. Currently, vaccines are **stored in a conventional vaccine refrigerator** in each NHGP's vaccination clinic room.

Proper vaccine storage and handling play critical roles in safely administering vaccines to prevent vaccine-preventable diseases. **Poor management of vaccine cold chain and vaccine administration can adversely affect vaccine efficacy, resulting in adverse health outcomes and financial loss** due to vaccine write-offs.

Problems/Challenges

1. Vaccines are **manually picked** by nurses and this **increases the risk of picking the wrong vaccine** for the patient.

2. As vaccines are stored in their respective baskets making the **expiry dates less visible**, it results in **potential wastage** when earlier batches of vaccines are not used first and **increases the risk of expired vaccines being administered**.

3. Nurses currently perform **many non-clinical tasks**, which take about 45 minutes daily. This includes counting the number of vaccines, ensuring timely stock up, arranging and rearranging vaccines according to expiry dates to attempt to ensure first expiry first out, changing the temperature chart, monitoring vaccine expiry dates, etc.

4. The conventional vaccine refrigerator is connected to a temperature monitoring logger to ensure optimal vaccine storage conditions and to facilitate cold chain monitoring. There is also a backup uninterrupted power supply (UPS) with 2 hours of backup power supply for contingencies like power outages. The UPS is exposed and sited next to the conventional vaccine refrigerator, which puts it at **risk of being accidentally powered off by patients or other non-healthcare staff.**

Findings/Solutions

The SMARTVacc or Safety Manpower Productivity Accountability Real-Time Analytics Vaccine System is Singapore's **first intelligent fully-automated vaccine management system. It won the 2019 Open Innovation Challenge (OIC)** organised by NHG Centre for Medical Technologies and Innovations (CMTi) and Enterprise Singapore. Conceptualised by NHGP and our partner, DROP Positioning Systems, Kallang Polyclinic is the first polyclinic to conduct a proof-of-concept testing of this prototype system.

Staff Nurse Lim Gek Swee showcasing the features of SMARTVacc to Health Minister Mr Ong Ye Kung during Kallang Polyclinic official opening event (Source: MOH's Facebook Page – 7 May 2022)

Staff Nurse Lim Gek Swee performing validation check to ensure correct vaccine (Source: screen grab from CNA – 7 May 2022)

Safety

SMARTVacc reduces potential human-related vaccination errors with an artificial intelligence-based vaccine image recognition system. The image camera recognition system safely **validates the accuracy of vaccines picked for dispensing before administration**. Expired vaccines are also locked automatically and prevented from being dispensed. This **reduces the risks of human-related vaccination errors and further enhances patient safety**.

Manpower Productivity

During the pilot, the nurses' **time spent on non-clinical tasks has also been greatly reduced** by approximately 21 hours per month per SMARTVacc system. With Real-Time Inventory Management and Cold-Chain Monitoring, nurses no longer need to count vaccine stocks or perform other manual non-clinical tasks related to vaccine administration. This allows the nurses to spend **more time on patient care, resulting in increased clinical productivity.** This time saved could potentially help to create additional Vaccination Clinic Appointments slots. Overall, manpower productivity and efficiency have been enhanced.

Accountability

SMARTVacc is a fully secured system, and the **vaccines are protected from access by an unauthorised party**, as only authorised users can dispense them through a fingerprint reader. Work processes according to policies are now enforced, which improves staff discipline and adherence. SMARTVacc stores the last transaction status if a staff bypasses any vaccine validation process (whether by accident or deliberate action), which **enforces process compliance. Every event is recorded** and may be used for audit purposes or future reference.

Real-Time Analytics

Real-time Digital Inventory and Cold-Chain Management Systems **eliminate all current manual tracking processes**. The inventory stock report will **monitor the vaccine inventory in real-time,** which makes stock checking very robust. This can even be applied

across multiple machines for a cluster overview of current stocks and needs. Vaccines that are low in stocks are highlighted, ensuring that **reordering of vaccines is done timely. Vaccine wastage can be significantly reduced with the First-Expired-First-Out (FEFO) feature. Vaccine viability and patient safety are also ensured** as the cold-chain is monitored via real-time temperature tracking, and any temperature transgressions are recorded and highlighted immediately.

Current Status/Future Plans

With the successful pilot and conclusion of the proof-of-concept phase in Kallang Polyclinic, the project team plans to **develop a new SMARTVacc system and conduct proof of value testing** together with other Public Healthcare Institutions.

The new SMARTVacc system is envisioned to have additional functionalities and intelligent features to **enhance patient safety, improve manpower productivity and efficiency, and integrate with the NEXT Generation Electronic Medical Records (NGEMR).** It will also be more compact and better suited to the space constraints of a Polyclinic vaccination clinic room.

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A4 | THE BIG STORY

Kallang Polyclinic piloting automated vaccine management

Facility also boasts self-service blood pressure machines among range of healthcare services

We must work on areas of improvement that may be less pressing, but more important - which is to make ourselves healthier.

Source: The Sunday Times – 8 May 2022

New Kallang Polyclinic to pilot automated vaccine management system to ensure patient safety

Similar to a vending machine, the SMARTVacc allows nurses to select from different types of vaccines for patients. ST PHOTO: KUA CHEE SIONG

Source: TNP – 7 May 2022

NHGP Nursing team with SMARTVacc during Kallang Polyclinic official opening event

Tunable Display of Protein Nanocages for the Management of Hyperpigmentation Skin Condition

Problems/Challenges

Skin is the largest organ of the human body which acts as the first line of defense against many external factors such as UV radiation, foreign particles, pathogens and allergens. The major component of skin consists of keratinocytes, in the epidermal layer at different stages of differentiation, along with an extracellular matrix composed of cross-linked proteins and lipids. This tough matrix hinders the transport of drugs and other molecules into the skin. **Drugs or cosmetic active ingredients for managing skin conditions are typically delivered trans-dermally and designed for slow and sustained release.** These active ingredients are required to achieve the desired depth of penetration and have to act over a specific period without causing any side effects. However, this is seldom achieved. It has been observed that these active ingredients when delivered on to the skin, **leads to complications such as depigmentation, irritation, and dermatitis, due to the lack of specificity and penetration properties of conventional carrier molecules.**

Findings/Solutions

Self-assembling protein nanocages (PNCs) forming hollow structures are explored as potential carriers in various nanotechnology applications. Nature-derived protein cages such as E2 (from *Bacillus stearothermophilus* E2 core domain of pyruvate dehydrogenase enzyme) and ferritin (from *Archaeoglobus fulgidus*) with intrinsic self-assembling properties have **tunable structural and functional characteristics which can be engineered to suit various biological applications.** In this project, E2 protein nanocages are engineered and used as shuttles for drug delivery to skin cells. Targeting and penetration peptides are genetically fused to these E2 nanocages for **generating functionalised protein nanocages to enhance penetration through the skin layers and deliver active molecules to target cells of interest, for the management of hyperpigmentation** (Figure 1).

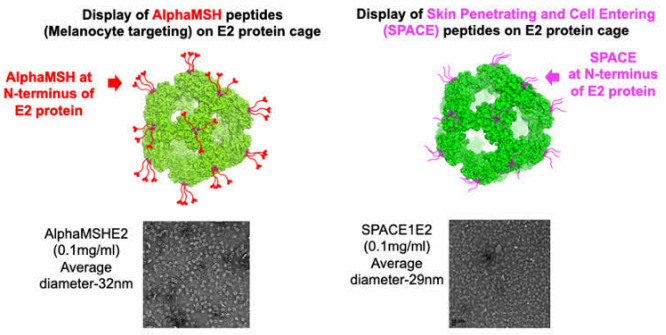


Figure 1: Modifications of E2 protein nanocages to display targeting and penetration peptides

The in-vitro cell-uptake assay data showed that **the uptake efficiency is higher in SPACE modified E2LC2 than the blank E2LC2 protein cages**, in particular the SPACE2E2LC2 protein cages are more efficient in penetrating the skin cells. The cell uptake of proteins starts in less than half an hour of incubation time and reaches 90% in keratinocytes in 3 hours. **The E2 protein cage**

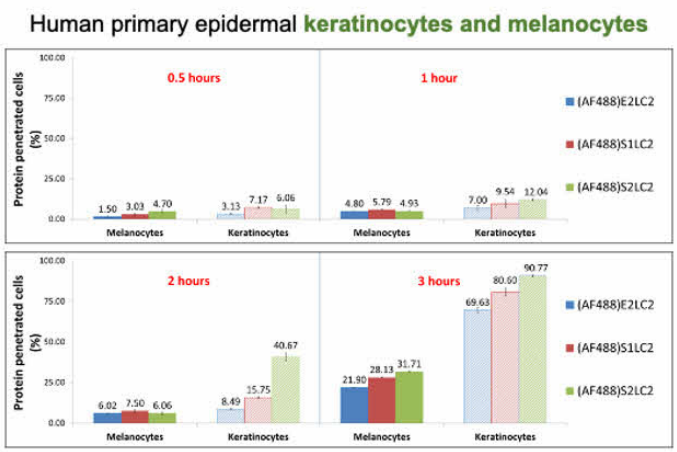


Figure 2: Enhanced cell uptake efficiency of E2 protein nanocages modified with penetrating peptides S1 and S2

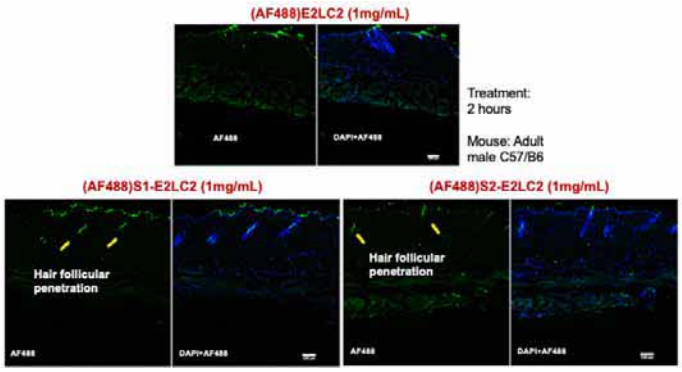


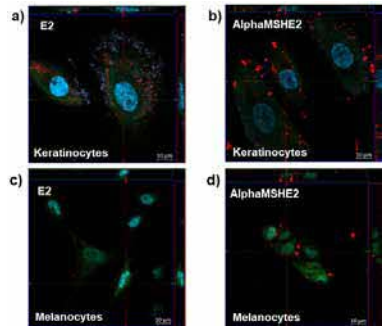
Figure 3: In-vivo skin penetration of 1mg/ml (AF488) SPACE1E2LC2, (AF488) SPACE2E2LC2 and the blank (AF488) E2LC2 proteins in mouse skin

penetrates keratinocytes better than the melanocytes as showed in the graph (Figure 2). In the melanocytes, only 31% penetration is observed in SPACE2E2LC2 and SPACE1E2LC2 while E2LC2 has even less cellular penetration. **The penetration trend observed in keratinocytes is the same in the case of melanocytes even though the overall coverage of cells is less significant.**

The confocal imaging of the mouse skin samples incubated with E2LC2 and SPACE E2LC2 PNCs shows that the engineered PNCs SPACE1E2LC2 and SPACE2E2LC2 proteins have accumulated in the hair follicles below the topmost layer of the epidermis in 2 hours of incubation time (Figure 3). **Recent investigations in skin research shows that the trans-appendageal route that consists of hair follicles, sweat glands and sebaceous glands is an efficient pathway for the penetration of topically administered therapeutics.** These appendages can act as a reservoir for the carriers and aid their permeation through the skin.

The study team has engineered E2 PNCs with AlphaMSH targeting ligand for melanocyte cell specific delivery. **The AlphaMSH peptide sequence is known to interact with MC1R receptor on melanocytes to aid targeting.** The confocal imaging shows that the **AlphaMSHE2 PNCs are taken-up by both the cell types at a higher rate compared with the E2 PNCs.** The enhancement of cell uptake of the E2 PNCs by the addition of AlphaMSH ligand can be clearly seen in melanocytes (Figure 4). The flow cytometric quantification of the percentage of cells that has taken up the PNCs (Figure 5) shows that the PNCs are taken-up at concentration as low as 100pM in 0.5 h. Almost 100% of the cells take-up the PNCs at 500pM in 2 hours of application. Hence, the comparisons are restricted to 100–500pM concentration and 0.5–2 h time limits. AlphaMSHE2 is taken up by all cell types including keratinocytes (Figure 5a–c) with higher efficiency than bare E2. Figure 5c shows that the difference in uptake of AlphaMSHE2 and E2 is significant for melanocytes at 250pM in 1 and 2 h, and at all-time points at 500pM. At 500pM PNCs, the cellular uptake of AlphaMSHE2 by melanocytes is 4-fold higher than bare E2 in 2 hours.

The data suggests that there is an obvious involvement of a receptor for endocytosis in melanocytes that enhances the differential uptake up to 12 times compared with keratinocytes at 500pM (Figure 5). It is observed that there is a concentration-dependent uptake of the PNCs carrying the AlphaMSH ligand. The team has conducted experiments on the mechanism of uptake to show the receptor mediated endocytosis of AlphaMSHE2PNCs (Bhaskar S, Lim S et al., Adv. NanoBiomed Res, 2021).



Confocal Z-stack position: centre
Channels:
Blue - DAPI
Green – Cytotracker
Red – AF594 (PNCs)

Figure 4: Confocal microscopy images of skin cell uptake of 5nM PNCs (red) in 2 hours: Nucleus stained with DAPI (blue), and Cytotracker (green). a) Primary epidermal keratinocytes incubated with E2 PNCs. b) Primary epidermal keratinocytes incubated with AlphaMSHE2 PNCs. c) Primary epidermal melanocytes incubated with E2 PNCs. d) Primary epidermal melanocytes incubated with AlphaMSHE2 PNCs (Bhaskar S, Lim S et al., Adv. NanoBiomed Res, 2021)

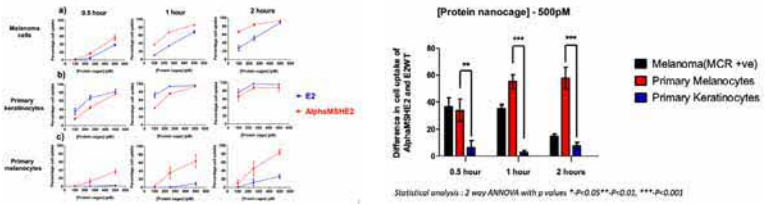


*Figure 5: Flow cytometric assessment of cell uptake of E2 and AlphaMSHE2 PNCs: a) Percentage cell uptake of 100pM, 250pM and 500pM of E2, AlphaMSHE2 in primary epidermal keratinocytes in 0.5, 1, and 2 hours. b) Percentage cell uptake of 100pM to 500pM E2 and AlphaMSHE2 in primary epidermal melanocytes in 0.5, 1, and 2 hours. c) Percentage cell uptake of 100pM to 500pM E2 and AlphaMSHE2 in G-361 melanoma cell line in 0.5, 1, and 2 hours. d) Difference in percentage cell uptake between AlphaMSHE2L2 and E2 in keratinocytes, melanocytes, and melanoma cells in the study. Cell uptake is expressed in terms of the percentage of cells with fluorescence from AF594 conjugated to the PNCs ± SEM for N = 3 (where N is the number of independent experiments each performed in triplicates). Statistical analysis: two-way ANOVA with p values *-P<0.05**-P<0.01, ***-P<0.001 (Bhaskar S, Lim S et al., Adv. NanoBiomed Res, 2021)*

Conclusions

PNCs are potential delivery vehicles that can be engineered with penetration and targeting ligands for skin applications. The **addition of the SPACE peptide to E2 PNCs increased the cell uptake efficiency in both keratinocytes and melanocytes.** The penetration study with mouse skin shows that the SPACE engineered E2 PNCs follow the trans-appendageal pathway of penetration through the skin in comparison to the bare E2 PNCs which shows no significant penetration.

AlphaMSH engineered E2 PNCs shows a maximum of 12-fold enhanced uptake in melanocytes in 2 hours of incubation time compared to bare E2 PNCs through AlphaMSH receptor mediated endocytosis. This shows the **targeted enhancement of the uptake of PNCs in melanocytes that can be leveraged to deliver drugs and active molecules for the management of hyperpigmentation.**

Current Status/Future Plans

The study team has **showed the increase in penetration and targeting efficiency of PNCs by displaying penetration and targeting ligands respectively**. The PNCs are now formulated with generic active molecules for the management of hyperpigmentation and stress induced aging. The team has patented the technology for engineering PNCs for targeting melanocytes and have a know-how for the formulation of generic active molecules with PNCs. The study team is **exploring the commercial potential of PNC based active molecular formulation for skin and health care applications.**

Patents and Publications

- Sierin Lim, Sathya Moorthy Bhaskar, Steven Thng, Ambili Kuniyil, Sarker Mridul; "Targeting of Melanocytes for Delivering Therapeutic or Diagnostic Agents Using Protein Nanocages", 2022. (EP, USA, IL).
- A know-how has been filed in NTUitive, titled as "Formulation of active molecules in protein cages" NTU Ref. No. 2019-337.
- Sierin Lim, Tomczak Nikodem, Sarker Mridul; "Protein Nanocage-stabilized Pickering Emulsions and the Use Thereof", 2017.
- Bhaskar, S., Lim, S. "Engineering protein nanocages as carriers for biomedical applications". NPG Asia Mater 9, e371 (2017)
- Bhaskar S, Lim S et al., "Engineering protein nanocages for the targeted enhancement of melanocyte cell uptake for the management of hyperpigmentation", Adv. NanoBiomed Res (2021).
- Sarker, Lim, S, et al., "Supramolecular Protein Assembly Retains Its Structural Integrity at Liquid–Liquid Interface" Adv. Mater. Interfaces,7 (2020).
- Sarker M, Lim S, et al., "Protein Nanocage as a pH-Switchable Pickering Emulsifier" ACS Appl Mater Interfaces 2017, 9 (12), 11193-11201.

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Developing Novel Keratin Templates as Dermal Equivalents - A Preclinical Study

Problems/Challenges

There is a high global demand for transplantable skin. Yet existing skin-equivalent products come with several shortcomings, including high costs, poor graft takes, high infection rates, immunological reactions to animal materials and risk of inter-species pathogen transfers. A research group from Nanyang Technological University (NTU) had developed a novel potential skin equivalent template by chemically cross-linking human hair keratin with alginate. Preliminary studies using a subcutaneous implantation model suggest that the **keratin-alginate template encourages superior stroma cell infiltration, tissue in-growth and neovasculature formation**. The team now embarked on a pre-clinical, in-vivo study testing the keratin-alginate template in a porcine model of deep partial-thickness burns. This project was a collaboration between NTU, NSC, Singapore General Hospital (SGH) and Skin Research Institute of Singapore – Agency for Science Technology and Research (SRIS – A*STAR). It was funded by the A*STAR-NHG-NTU Skin Research Grant.

Findings/Solutions

Human hair samples were collected and processed to extract keratins. These were **cross-linked to commercially available alginates to yield the keratin-alginate templates** before freeze-drying them into dry sponges for the animal studies. Standardised deep partial-thickness burn wounds were created on sedated pigs used in the study. **Each wound was randomised to one of the following treatment arms: 1) None (control); 2) Application of keratin-alginate sponge; 3) Application of commercially-available dermal substitute (Pelnac™); and 4) Allograft**. Wounds were serially imaged digitally to monitor for percentage of dermal substitute incorporation. Transverse sections were also cut at serial time points and processed for routine histology and immunohistochemical staining for expression of markers of skin viability, integrity, lymphocyte infiltration, and fibrosis.

Initial problems encountered included **unexpected early degradation of keratin-alginate sponges, as well as difficulty with handling circular-shaped wounds**. These were overcome with modifications made to the fabrication of keratin sponges, and also adoption of square wounds. The keratin-alginate sponges seemed to **provide similar healing compared to commercially-available dermal substitutes and allograft**. Epidermal regeneration was noted from day 14 onwards in all three groups, with complete regeneration observed by day 44. The **keratin-alginate sponge supported faster re-epithelialisation and wound closure than other treatments** (Figure 1). Efficacy of re-epithelialisation was corroborated by positive cytokeratin immunohistochemical stains (AE 1/3), while expression of smooth muscle actin indicated angiogenesis due to the presence of mature blood vessels in the dermis. **Keratin-alginate sponges did not cause any host tissue immune response based on clinical observations**. Unlike the control group, wounds treated with keratin-alginate sponges did not exhibit thick eschar formation.

Current Status/Future Plans

It is found that the **keratin-alginate sponges are potentially suitable for clinical exploitation as dermal substitutes**. This can be further explored in human clinical trials.

Publication

Moay ZK, Nguyen LTH, Hartrianti P, Lunny DP, Leavesley D, Kok YO, Chong SJ, Chua AWC, Tee S-I, Ng KW. Keratin-Alginate Sponges Support Healing of Partial-Thickness Burns. *International Journal of Molecular Sciences* 22(16):8594, 2021.

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Dr Chong Si Jack, SGH
Assoc Prof David Leavesley, SRIS

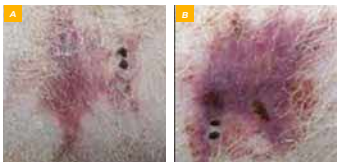

Figure 1: 51st post-operative day. The keratin-alginate templates showed good wound re-epithelialisation (A) compared to control wound (B).

The Important Role of Biostatistics in Advancing Mental Health Research

Biostatistics comprises a specialised methodology for collecting and analysing biomedical and healthcare data (Rossi, 2022). **The role of biostatistics in research is not limited to data analysis but one that is involved in every stage of research process** starting from study conceptualisation, study design, sample size estimation and consideration of the relevant statistical methods for ensuring the high-quality of research publications and dissemination of research findings accurately (Zapf et al, 2020). **In the initial stages of the study, addressing basic statistical concepts are crucial to ensure that the study design is feasible and for avoiding bias**. It also ensures that the study aims are measurable and reliable and the sample is representative and sufficiently powered to make statistical inference (Kishore et al 2022; Zapf et al, 2020). **During the final stages of data analysis and dissemination of research findings, biostatistics knowledge is essential to ensure that the data is analysed using appropriate statistical models**, translating statistical methodology so that statistical terminology is easily understood, identifying limitation of the data, ensuring the interpretation of analyses are robust and accurate and finally supporting the principal investigator to address any queries from reviewers related to statistical method used in the study (Vonthein et al, 2020).

Over the recent years, the amount of data captured has increased from electronic health records/mobile apps, data sharing/linkages across healthcare institutions, growing pool of epidemiological surveys, focus on patient reported outcomes and **capturing the impact of coronavirus pandemic on multiple domains of health**, which has highlighted the role of biostatisticians and biostatistical scientists (Zelen, 2003). **The role of biostatistics is increasingly important especially in supporting mental health research to transform the understanding and treatment of mental illness across many different research areas spanning from basic to clinical research**. Increasing number of statistical methods have been developed and employed. These include using more complex statistical models such as complex survey analysis, statistical genetics, causal inference, multivariate analysis, machine learning, psychometrics and latent variable modelling in order to support advancing clinical research, trials, validation of instruments and risk prediction and psychiatric epidemiology surveys in the mental health field.

In IMH, my work comprises providing statistical support to our researchers throughout their research journeys, collaborating with epidemiologists, psychometricians and health economists to advance mental health research in Singapore, **initiating my own studies that leverage on complex statistical analysis and lastly, mentoring young researchers who are increasingly interested in pursuing this field of research**.

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Chicken Soup for the Busy Coordinator

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- Meticulous and possess good analytical skills for reviewing research protocols in a timely manner.
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