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07 BREAKTHROUGHS

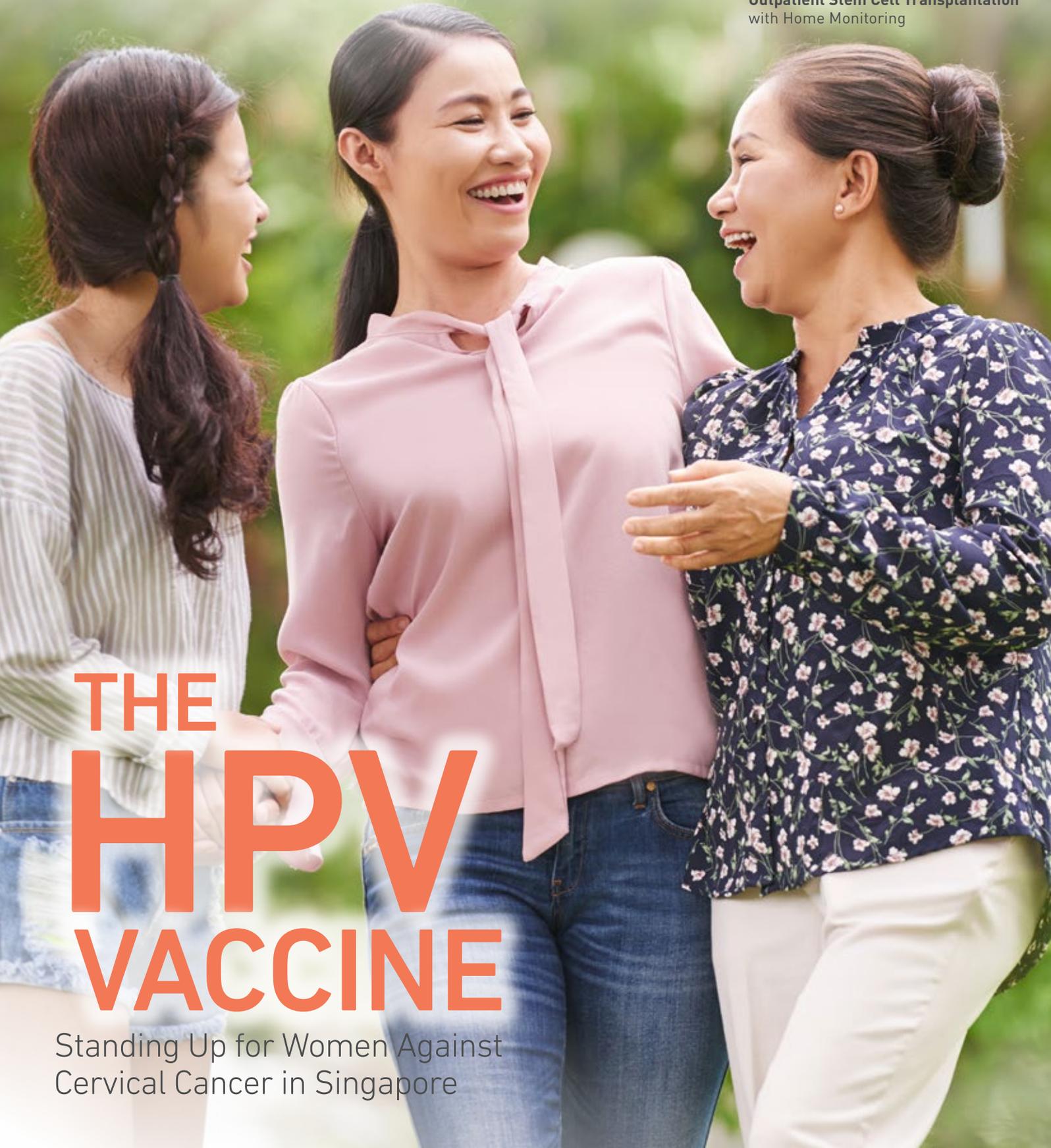
PIPAC - A New Weapon in the Treatment for Peritoneal Carcinomatosis

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Next Generation Imaging Mass Spectrometry; A Paradigm Shift in Cancer Imaging

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Outpatient Stem Cell Transplantation with Home Monitoring



THE HPV VACCINE

Standing Up for Women Against
Cervical Cancer in Singapore

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Dear friends and colleagues,

Welcome to the 7th issue of SPARK! We kick off this issue with cervical cancer awareness and the vaccination for human papillomavirus (HPV). It is important to know that cervical cancer can be prevented with HPV vaccination and regular cervical cancer screening. The national HPV vaccination programme has been launched in Singapore secondary schools and vaccinations are made affordable with MediSave coverage, so there is no excuse that we cannot have our young generation vaccinated to prevent this silent killer!

We also shine the spotlight on our haematology division in our special feature and education sections of this issue. The outpatient stem cell transplantation with home-based care programme (page 11) is a unique, new model of care. It is testament that with regular follow-up and a close working relationship between the healthcare team and the patient and family, home-based care can be performed safely and improves the quality of life of our patients. After all, "home is where the heart is" so, why not bring healthcare to one's home in their time of need? With such an innovative programme, we hope to inspire and train our next generation of haematologists through our Haematology Senior Residency Programme (page 16) and we look into a day in the life of a Haematology Senior Resident (page 17).

This issue also features three great cancer research programmes in NCIS and the Cancer Science Institute of Singapore (CSI), one of which is our PIPAC (Pressurised Intraperitoneal Aerosol Chemotherapy) treatment for peritoneal carcinomatosis (page 7). The Peritoneal Tumour Study Group @ NCIS is the pioneer in the region to bring this new "weapon" in the fight against peritoneal metastasis, which carries a poor prognosis. We also highlight new technology with the next generation imaging mass spectrometry (IMS), which looks at spatial distribution of the molecular content within the tissue (page 9). In collaboration with the PIPAC programme, our investigators are then able to interrogate the depth of pressurised chemotherapy penetration in tissue using IMS in PIPAC. This collaborative effort between the two research groups clearly exemplifies the strength of NCIS in bringing our researchers together! Another form of imaging known as multispectral microscopy to investigate markers in several DNA repair pathways is an area of expertise by our partners at CSI and we look into their work on DNA repair in our CSI showcase section (page 15). DNA repair is an area of hot interest especially with the availability of DNA repair inhibitors for clinical use.

"It is important to know that cervical cancer can be prevented with HPV vaccination and regular cervical cancer screening. The national HPV vaccination programme has been launched in Singapore secondary schools and vaccinations are made affordable with MediSave coverage, so there is no excuse that we cannot have our young generation vaccinated to prevent this silent killer!"



I hope that you enjoy reading this issue as much as I have working with our great editorial team in putting it together. We look forward to more achievements in the rest of 2019 as we continue our fight against cancer!

Dr Chee Cheng Ean

Senior Consultant
Chief Medical Editor



THE HPV VACCINE:

Standing Up for Women Against Cervical Cancer in Singapore

In May 2018, the World Health Organization's (WHO) Director General made an important call for the world to commit to a total eradication of cervical cancer⁽¹⁾. In a timely move towards WHO's goal, the Ministry of Health (MOH) announced on 6 March 2019, the launch of the free Human Papillomavirus (HPV) vaccination programme for Secondary 1 girls in national schools. Singapore now stands alongside 50 other countries, such as Australia, Canada, Finland,

Sweden, Malaysia and the United Kingdom in the global fight against cervical cancer.

Along with this announcement, MOH has also introduced a more sensitive cervical cancer screening tool to detect pre-cancerous cervical lesions. The HPV DNA test will be the new national cervical cancer screening strategy for women aged between 30 and 69 years old.

Why is cervical cancer prevention important?

Cervical cancer is a silent killer. It usually has no symptoms and when the symptoms do manifest, the cancer is already in its late stages. Despite having an effective vaccine and screening tool, cervical cancer remains an epidemic worldwide, coming in as the fourth most common gynaecological cancer globally, especially in developing countries^[2, 7].

Cervical cancer incidence in Singapore has shown a decline following the introduction of the national cervical cancer screening programme in 2004. However, it remains the 10th most commonly diagnosed cancer among women. In addition, a worrying upward trend can be seen from the latest Singapore Cancer Registry report (2011-2015)^[3]. The recent MOH national survey also showed an increase in Singaporean women aged 30 years old and above being diagnosed with late-stage cervical cancer, with no improvements in the uptake of cervical cancer screening among Singaporean women^[4].

While cervical cancer screening remains a pivotal player in the prevention of this disease, it has to work together with an effective HPV vaccination programme. See Table 1 for the list of preventive recommendations.

The virus that changed the world

The HPV is a group of double stranded DNA viruses which are extremely common worldwide and can be

transmitted through skin contact including genital contact. Hence, women and men who are sexually active will be infected by this virus at some point in their life. This does not mean that penetrative sex is a necessity for transmission^[5].

There are more than 100 types of HPV and from these, 14 of them are currently recognised to cause cancer (oncogenic HPV). Among them are the HPV 16 and 18, which are known to cause 70 per cent of cervical cancer and precancerous lesions. Acute infection including cancer-causing HPV infection does not increase the risk of developing cervical cancer. The issue lies in the persistence of the HPV infection^[6, 7].

Key facts on HPV vaccine for cervical cancer prevention

The HPV vaccine is a prophylactic vaccine. It works by protecting the host against future cancer-causing HPV infections. It is a viral-like particle (VLP) which means that it is made up of a protein coat with no viral DNA in the vaccine. This allows the vaccine to confer immunity without the ability to infect the host. It has a strong safety profile and to date, the most reported adverse effect is pain at the injection site.

There are three HPV vaccines available worldwide; the bivalent, quadrivalent and nonavalent. While all the vaccines cover HPV 16 and 18 with similar effectiveness, the difference lies in the amount of protection that each vaccine can provide. This is illustrated in Table 2 below.

HPV vaccination		Pap Test (Pap Smear)	HPV Test	
What is it?	Most effective if given before first sexual exposure, but also benefits those who are sexually active	Can benefit adults who have had previous exposure to cancer-causing HPV such as: <ul style="list-style-type: none"> - Those who are already sexually active before being vaccinated - Those who have had previous abnormal cervical screening results - Those who underwent treatment of pre-cancerous lesions 	Detects the presence of abnormal cell changes on the cervix due to cancer-causing HPV infection	Checks if there are any cancer-causing HPV strains on the cervix
Who is eligible?	9 to 26 years old females and males, regardless of sexual status	Approved by the FDA (U.S. Food and Drug Administration), the vaccine can be given to both females and males up to 45 years old	25 to 29 years old females who were previously and currently sexually active	30 years old and above females who were previously and currently sexually active
<i>(Females who have never had sex are not required to go for cervical screening)</i>				

Table 1: Preventive recommendations

HPV vaccine	Cervarix	Gardasil	Gardasil 9
Types of vaccine	Bivalent	Quadrivalent	Nanovalent
Cover for cancer-causing HPV infection	2 out of 14 HPV 16 and HPV 18	2 out of 14 HPV 16 and HPV 18	7 out of 14 HPV 16 and HPV 18 + HPV 31, 33, 45, 52 and 58
Protection from cervical cancer worldwide	Up to 70% protection	Up to 70 % protection	Up to 90% protection
Protection from non-cancer causing HPV (Genital warts)	No	Yes HPV 6 and HPV 11	Yes HPV 6 and HPV 11

Table 2: The different types of HPV vaccines available in Singapore and worldwide

FEATURE STORY

HPV vaccines are extremely effective in preventing the development of cervical cancer precursors, offering over 90 per cent protection^(8,9). But it is important to remember that none of these HPV vaccines will provide 100 per cent coverage. Hence, it is essential for women to be aware that regular cervical cancer screening must still be done because it can help to protect against other cancer-causing HPV infections that are not covered by the vaccine.

Protection is at its best if the vaccine is given before any exposure to the HPV infection. This is why adopting a school HPV vaccination programme is a crucial move towards the goal of eliminating cervical cancer^(10, 11).

In Singapore, the HPV vaccine is licensed to be given to young women aged 9 to 26 years old, with Medisave coverage of up to \$400 for the bivalent and quadrivalent HPV vaccines.

Women up to the age of 45 years old, who are already sexually active, with previous history of abnormal pap smear results or have been treated for precancerous

cervical lesions, may also benefit from the vaccine⁽¹²⁾. In October 2018, the Food and Drug Association (FDA) in USA has approved Gardasil 9 to be given to women up to 45 years of age.

HPV vaccination in Singaporean men

There is also emerging evidence of a causal relationship between an oncogenic HPV infection and the development of cancer of the anus, vulva, vagina, penis and oropharynx⁽¹³⁾ – especially HPV 16, which is known to increase the risk of anal, penile and oropharyngeal cancers in men.

In addition, there is emerging evidence regarding herd immunity and further reduction of cancer-related HPV infection in girls when the vaccination is also given to boys. Australia is an example of a country that has adopted a gender-neutral school HPV vaccination programme and this has resulted in the significant reduction of their cervical cancer and HPV infection rates. In Singapore, Gardasil and Gardasil 9 are licensed to be given to boys between 9 to 26 years old for protection against genital warts and anal precancerous lesions.

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Conclusion

Cervical cancer is unique in that we not only now know its main aetiology but its long natural history allows us to have an extremely effective prevention and screening tool to totally eradicate the disease in Singapore. However, education and awareness will also need to be an important aspect of our efforts⁽¹⁵⁾. It is not enough to just have these tools, as a nation we need to commit and execute these tools in the best possible way to empower and protect our women from this terrible disease.

This article was first published in Channel NewsAsia Online on 17 March 2019.



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Dr Ida Ismail-Pratt is a consultant at the Division of Gynaecologic Oncology, NCIS and a specialist in Obstetrics and Gynaecology at NUH, where she leads the Cancer Screening & Prevention Taskforce and the Gynaecology Cancer Screening & Prevention Programme.

She is a British Society for Colposcopy and Cervical Pathology (BSCCP) accredited colposcopist, whose special interest lies in cancer screening and prevention, Human Papillomavirus (HPV) and management of pre-invasive diseases. She spearheaded the introduction of the HPV DNA test and HPV primary screening for cervical cancer in NUH/NCIS since 2014, which is currently the new national cervical cancer screening programme.

PIPAC

(Pressurised Intraperitoneal Aerosol Chemotherapy)

A New Weapon in the Treatment for Peritoneal Carcinomatosis

Peritoneal carcinomatosis (PC) from various cancers carries a dismal prognosis with poor treatment outcomes. Following the diagnosis of PC, the treatment intent is often palliative. Many patients develop symptoms which are difficult to manage, including abdominal distension, intestinal obstruction and abdominal pain. The natural plasma-peritoneal barrier limits drug delivery from the systemic circulation into the peritoneal cavity, which further impairs the efficacy of systemic chemotherapy in the management of this miserable disease.

Specifically, for gastric cancer, many patients are diagnosed with PC at initial presentation where treatment options are limited. Recent data suggests that cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) has some efficacy for ovarian cancer but it is often not efficacious enough to warrant its significant morbidity and mortality risk for gastric cancer. The current treatment options for patients with gastric cancer presenting with PC include, systemic chemotherapy with or without targeted therapy, and intraperitoneal chemotherapy via an indwelling port. Yet, a significant proportion of patients still demonstrate disease progression despite receiving treatment.

Pressurised Intraperitoneal Aerosol Chemotherapy (PIPAC) is a novel drug delivery technique that directly delivers chemotherapeutic agents under high

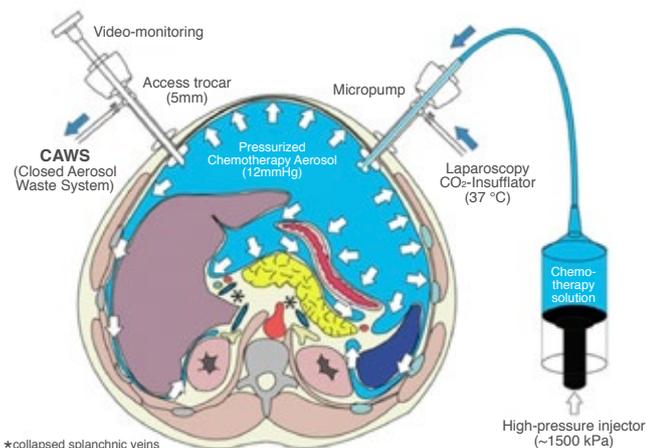


Figure 1

pressure directly into the peritoneal cavity. Taking advantage of physical laws such as aerosolisation and hydrostatic pressure, it ensures superior drug distribution and penetration to target PC (Figure 1). Furthermore, taking advantage of the plasma-peritoneal barrier, direct drug delivery into the peritoneal cavity limits systemic absorption and hence reduces the systemic toxicity from chemotherapy.

Drug Delivery

More than 3,000 PIPAC procedures have been performed worldwide and the procedure is highly standardised.

The patient is typically admitted for a day surgery procedure. In a negative-pressure operating theatre with laminar air flow, under general anaesthesia, a diagnostic laparoscopy will be performed (Figure 2). Following the confirmation and diagnosis of PC, and suitability of the patient's abdominal conditions, the aerosolising device will be set up and the chemotherapeutic agent will be delivered via PIPAC for a total of 30 minutes. After which, the chemotherapy aerosol is removed and the patient will be monitored overnight and discharged the following day.



Figure 2

BREAKTHROUGHS

Currently, PIPAC is a minimally-invasive palliative procedure that aims to prolong survival and preserve quality of life. Due to the low dosage applied, PIPAC can be combined with systemic palliative chemotherapy and has minimal organ toxicity. This procedure can be repeated at intervals of 6 weeks to 3 months.

Clinical Studies

On 12 December 2016, the first patient in Asia was treated with PIPAC using oxaliplatin by our team at NUHS under the proctorship of Professor Marc Reymond, from the University of Tübingen, Germany, who pioneered this procedure. The patient with pre-treated PC of gastric cancer origin, tolerated the procedure well with no toxicity nor adverse events, thus returning to her daily activities almost immediately after the procedure and maintaining a good quality of life. She went on and continued to have her second and third PIPAC procedures done successfully.

With this encouraging initial experience, we collaborated with medical oncologist Dr Yong Wei Peng from NCIS to develop a Phase-I dose escalating 3+3 protocol for treating patients with PC of gastrointestinal origin and obtained regulatory approval from the Health Sciences Authority of Singapore and Institutional Review Board (IRB) in 2016. At present, we have treated 15 patients with promising preliminary results so far.

Preclinical Studies

In addition to the early adoption of PIPAC for the treatment of PC, the multidisciplinary upper gastrointestinal cancer group at NCIS is also exploring the efficacy of PIPAC with other potentially suitable chemotherapeutic agents. To that end, we have conducted a preclinical study with paclitaxel, one of the most active anti-cancer agents. Being a large hydrophobic molecule, it is ideal for peritoneal administration as it is only gradually drained from the peritoneal lymphatics and therefore, it can accumulate to high concentrations to act on peritoneal metastases.

In collaboration with the National University of Singapore, we have initiated a preclinical animal study to assess the pharmacokinetic and toxicity profiles of PIPAC paclitaxel. We found that PIPAC paclitaxel demonstrated linear pharmacokinetic characteristics, with expectedly less systemic drug exposure and systemic toxicities. The study also provides the first data of the pharmacokinetics of PIPAC paclitaxel which will no doubt serve as a guide for future clinical trials. The results were presented at the annual scientific meeting of the Japanese Gastric Cancer Association (JCGA) and the International Gastric Cancer Congress (IGCC).



PIPAC Workshops and Demonstrations

To date, NCIS has conducted the first and second Asia-Pacific PIPAC symposium and workshop, to showcase our experience with this novel treatment. We are also pleased to host the first Congress of the International Society for the Study of the Pleura and Peritoneum later this year, from 29 to 30 November 2019.

Conclusion

While PC remains a challenging disease, PIPAC proves to be a promising and exciting new targeted treatment approach that may help our patients overcome this disease in the future.



Article by:
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Prof Jimmy So received his surgical training at the National University Hospital, Singapore, where he was trained in Upper Gastrointestinal (GI) Surgery, Surgical Oncology, Bariatric Surgery, Therapeutic Endoscopy and Minimally Invasive Surgery. He received fellowship training at Massachusetts General Hospital, Harvard Medical School, USA, and Royal Infirmary in Edinburgh, UK. His research interests include early diagnosis and novel treatment for gastroesophageal cancer and obesity. Prof So has published over 150 research articles and received many research grants for his research. He is one of the principal investigators of the Singapore Gastric Cancer Consortium. He was invited to speak at over 100 international and regional conferences including keynote lectures such as the Yahya Cohen Memorial Lecture by College of Surgeons, Singapore. He is also a member of the editorial board of scientific journals including Gastric Cancer and Journal of Gastric Cancer.



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On behalf of the Peritoneal Tumour Study Group @ NCIS

Next Generation Imaging Mass Spectrometry;

A PARADIGM SHIFT IN CANCER IMAGING

Mass spectrometry (MS) has long been the workhorse of protein and metabolite identification in translational research. The pioneering design earned a Nobel Prize in Chemistry in 2002 and has resulted in great advances in interrogating biological fluids for biomarker discovery, therapeutic targets, drug design and discovery, as well as systems biology. In 2003, the first experiment detailing the use of (MS) directly on tissue was performed. Using a 1mm² tissue, the authors were able to distinguish primary from metastatic lung cancer and good versus bad prognosis non small cell lung cancer by Imaging Mass Spectrometry (IMS). Specifically, this was achieved with the application of matrix solution on fresh frozen tissue prior to MS analysis, otherwise known as Matrix-Assisted Laser Desorption Ionisation (MALDI). The last two decades have seen an exponential growth in the technology and application of IMS in cancer research.

Mass spectrometry imaging allows for the calculation of the entire molecular content of the tissue section. By computational biology, the spatial distribution of the molecules can then be plotted with its corresponding intensity or relative abundance. This typically results in 100s to 1,000s of biomolecules per tissue section. Where historically a patient with a given tumour undergoes resection followed by pathological sampling, with IMS technology, we are now able to create biomolecular profiling at the peptide, lipid, protein, glycan,

metabolite level (Figure 1). With modern machines, this is achievable in near real time speed; an evolution in cancer research.

With the support of the National University of Singapore (NUS), National University Hospital, grant funding and industry collaboration, the SurgiCAL ProtEomics Laboratory (SCALPEL) was set up in February 2018. One aspect of the technology embraced here is the next generation of IMS. The technology is able to resolve biomolecules with a spatial distribution on tissue of 5µm in a matter of 45 minutes (in the first dimension of MS) per 2x2cm of tissue section. Following a period of protocols optimisation internally, we are currently embarking on a number of different projects as listed below. SCALPEL remains the only laboratory with an IMS technology within NUS and continues to grow and translate this technology further.

Underpinning this work is careful multidisciplinary workflow. Generating appropriate hypotheses where spatial distribution and identification on appropriate tissue targeting the class of biomolecule of interest remains integral. Clinical teams develop protocols for sampling of surgically resected or biopsied tissue is followed by pathological sectioning, annotation and allows for downstream IMS protocols. IMS experiments demonstrate the importance of collaborative work between clinicians and scientists; suited for expertise within the framework of NCIS.

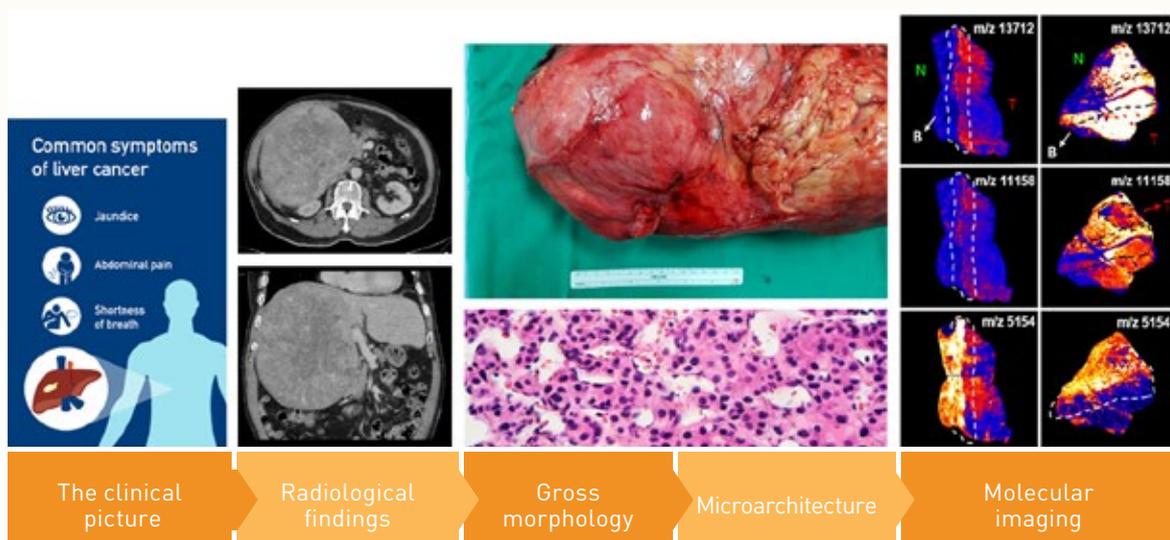


Figure 1: A paradigm shift in cancer imaging. Gleaning information from a patient, to radiological investigations, surgical resection, pathology and finally molecular profiling by IMS.

The clinical picture

Radiological findings

Gross morphology

Microarchitecture

Molecular imaging

DISCOVERIES

Specific Areas of Work

Hepatocellular Carcinoma (HCC)

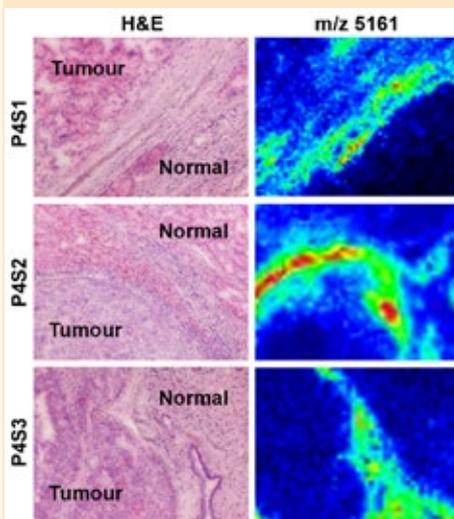


Figure 2: Three sections H and E stained slides of hepatocellular cancer tumour/normal boundaries (left) and corresponding IMS images (right). The expression of m/z 5161 is clearly seen to be distinctly abundant in the boundary of tumour and normal (most abundant = red, moderate abundance = green and least abundant = blue).

It has long been established that there is great tumour heterogeneity within HCC tumour tissue when interrogated by whole genome sequencing. Experiments in our laboratories have shifted the focus of this analysis to the tumour/normal boundary, the area histologically annotated to be normal, right next to the cancer resection margin. Here, we have seen far more consistent identities that are unique to this tumour/normal interface; uniquely different to tumour and uniquely different to normal (Figure 2). We have shown these to be immune proteins and thus provide a potentially unique understanding of the tumour biology as well as diagnostic/therapeutic target. Furthermore, our work with Dr Edward Chow at the Cancer Science Institute of Singapore (CSI) has shown that using an AI based platform on patient derived organoids (PDO)/xenografts (PDX) from HCC tissue, it is possible to rank drug combinations in chemosensitivity. IMS is applied directly on the PDO/PDX tissue to determine if molecular profiling of this tissue is able to inform therapeutic drug combinations.

Pancreatic Cancer

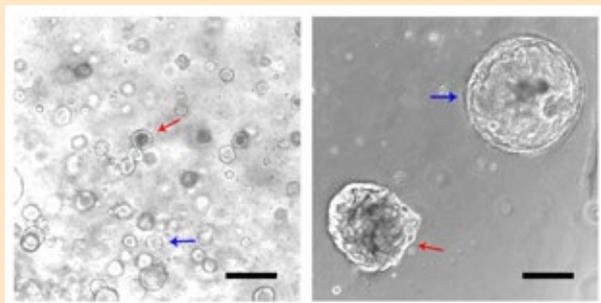


Figure 3: Human pancreatic ductal adenocarcinoma organoids from endoscopic ultrasound guided biopsies. Normal pancreatic organoids (blue arrow) with cystic morphologies and tumour organoids (red arrow) with filled morphologies. (Left) Day 8 (Right) Day 27. Scale bars, 200um.

We are currently undertaking an end to end translational study in pancreatic cancer with collaborators in NUH, NUS and NCIS. The hypothesis includes risk stratification of pancreatic cysts as well as personalising chemotherapy. At SCALPEL, we use fine needle

aspirations of the cancer tissue obtained at Endoscopic Ultrasound Scanning, to successfully grow PDOs of pancreatic cancer (Figure 3). From this, we aim to assess chemosensitivity and thereby more effectively target treatment for this aggressive cancer. More importantly, even when resectable, 70% of patients undergoing surgery will recur in 3 years. We aim to better target neoadjuvant and adjuvant chemotherapy, thereby improving outcomes in resectable disease.

Machine learning in Mass Spectrometry

While IMS technology continues to improve spatial resolution of biomolecules with increasing sensitivity, the resultant data is enormous. Typically, 1 section of tissue from 1 tumour can result in 1.5 billion m/z species representing 1,000s of biomolecules. Historically, IMS companies have developed proprietary and freeware software to provide solutions for data analysis. More recently, machine learning has been increasingly utilised. Our work, in-house in this area has shown promising results for such solutions to fully automate IMS pipelines.

Pressurised IntraPeritoneal Aerosolised Chemotherapy (PIPAC)

While the trials are currently underway with promising results, this form of chemotherapy is postulated to be effective by increasing drug penetration at the site of delivery, while maintaining a relatively low systemic concentration; thereby increasing efficacy with minimising side effects. Using IMS, for the first time, we are able to interrogate the depth of penetration of aerosolised chemotherapy in a porcine model. Perhaps more importantly, the real time nature of our technology would mean that drug concentration may be detailed and therefore inform dosing.



Article by
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Dr Glenn Kunnath Bonney attained his undergraduate medical degree in 2002 from the University of Leeds. Having completed Basic Surgical Training, he was awarded the Membership of the Royal College of Surgeons of England (MRCS) in 2006. He then undertook a postgraduate research degree at the Cancer Research UK, where his proteomic-based research culminated in a Doctorate of Medicine (MD) in 2008. He completed his specialist training at the University Hospitals of Birmingham and became a Fellow of the Royal College of Surgeons of England in 2014. His clinical research has resulted in him receiving the Presidential Award of the International Hepatopancreaticobiliary Association in the same year.

Dr Glenn joined the National University Hospital in 2016 and is a currently a liver, pancreas and transplant surgeon. In February 2018, with the support of NUH and NUS, he started the SurgiCAL ProtEomics Laboratory (SCALPEL) in NUS with a focus on using proteomics technologies in the clinical arena. The team has expertise in proteomics, analytical chemistry, organoids, machine learning and molecular biology.

OUTPATIENT STEM CELL TRANSPLANTATION

with Home-based Care

When the need for stem cell transplantation was explained to Mr Y who was diagnosed with multiple myeloma, his primary concerns apart from the procedural risks, were that of the one-month stay in the hospital and the valuable time spent away from his family. Hence, he readily agreed at the option of having his post-transplant care done at home with the clinician and nursing team visiting him for follow-up appointments.

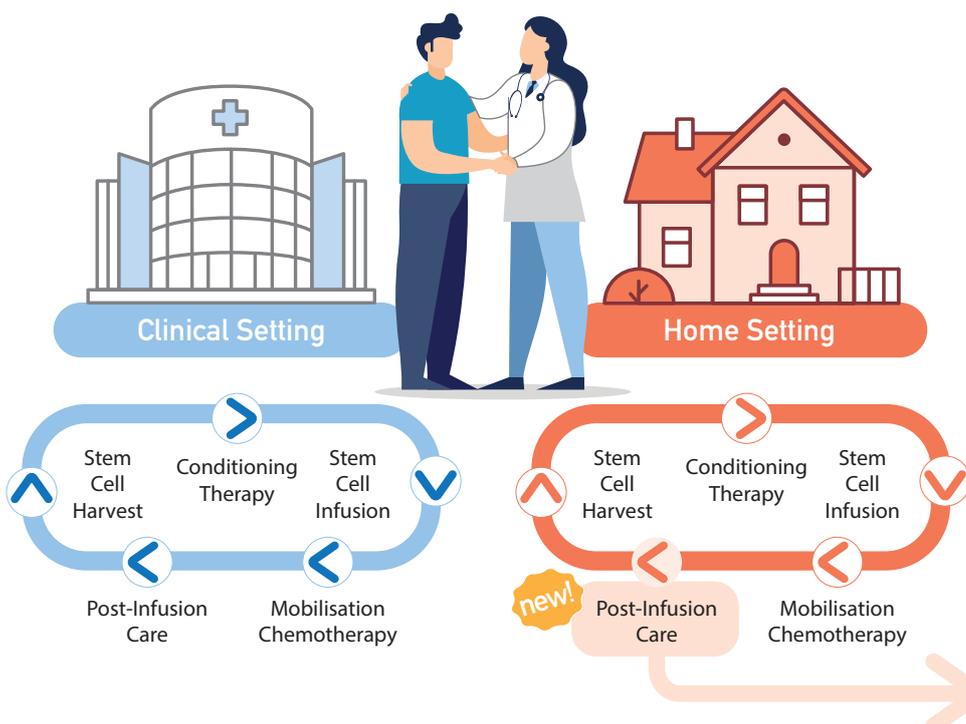
Mr Y went on to become the first case to undergo this new model of care in January 2018. His transplantation procedure went smoothly and he did not require any admissions throughout this period. More importantly, this new home-based approach has allowed him to spend what was a potentially stressful period in the comfort of his own home, with his family around to support him. In light of the recent changes in the Ministry of Health (MOH) financing policy to support outpatient initiatives such as this, Mr Y was also able to benefit from the minimal out-of-pocket charges for his procedure.

Myeloma and Autologous Transplantation

Myeloma is a type of bone marrow cancer characterised by abnormal expansion of malignant plasma cells in the bone marrow. The treatment for myeloma includes induction therapy, using a cocktail of drugs to kill the fast-growing plasma cells. This is then usually followed by an autologous stem cell transplantation (ASCT), which allows the patient to receive high doses of chemotherapy.

In ASCT, stem cells are collected from the patient prior to the initiation of the high-dose chemotherapy and are then frozen and stored. High doses of chemotherapy are then given to destroy both the myeloma cells and the healthy blood cells in the bone marrow. After this treatment, the healthy stem cells are reinfused through a vein. New blood cells are then developed from the transplanted stem cells so that they can replace the ones that were destroyed by the treatment. The time taken for counts recovery from stem cell infusion is usually about 10 days.

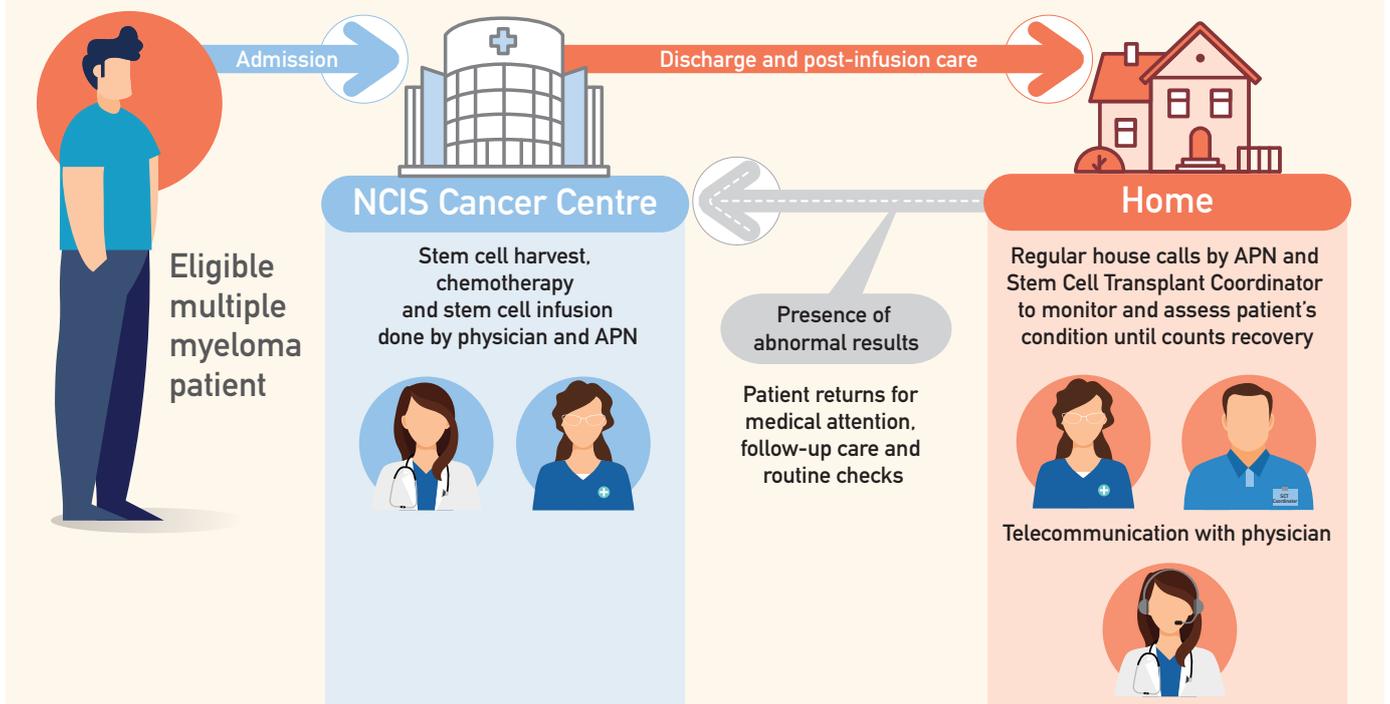
Traditional versus New Model of Care



Benefits to Patients and Caregivers

- Saves money
- Minimal disruption to daily lives
- No waiting time
- No travelling time
- Less time off work
- Enjoy greater comfort
- Promote quality of life
- Lower risk for hospital acquired infection

ASCT with Home Monitoring Patient Journey



ASCT has traditionally been done in the hospital setting, where patients stay for about two to four weeks following the use of strong doses of chemotherapy to kill the cancer cells. The main purpose of hospitalisation is to provide supportive care during the period of mucositis and cytopenias when the risks of infection may be high. What is increasingly being recognised however, is that inpatient transplantation may be associated with increased healthcare costs, greater utilisation of inpatient resources and increased risks of iatrogenic complications such as nosocomial infections. Among the various indications for transplantation, ASCT for myeloma has been particularly amenable to an outpatient model. Factors allowing for this include its lower intensity compared to the other types of transplantations, short conditioning (single day of high-dose melphalan chemotherapy), shorter period of myelosuppression, predictable engraftment kinetics, as well as reduced transplant related toxicities.

Led by Prof Chng Wee Joo, NCIS has been offering outpatient ASCT for selected patients with multiple myeloma since 2011. Following high-dose chemotherapy, patients are allowed to go home and are only required to return to the clinic regularly for blood checks and clinical review. In a retrospective review done in 2017, looking at outcome measures for these transplants, Prof Chng and our team from NCIS were able to demonstrate the feasibility and lower complication rates in these patients, compared to those who underwent the traditional model of inpatient transplantation. In addition, these transplants were also found to be cost-effective, with treatment costs for patients being reduced substantially by up to 20 to 30 per cent. More importantly, the feedback from the patients and their caregivers was encouraging, most of

whom were comforted to be able to avoid a 3-week isolated stay and being away from their loved ones.

With this outpatient model of myeloma ASCT established, the natural next step forward for the team has been to incorporate home-based care into the treatment model. Pioneering results from the Karolinska Institute in Sweden and Duke Hospital have shown that home-based models of care is effective in reducing infective complications and improving the patients' quality of life.

In our model, the NCIS team will first perform a home assessment prior, to ensure safety and adequacy of the home setup. Following the chemotherapy conditioning and stem cell infusion done in NCIS Cancer Centre, subsequent monitoring until counts recovery will be transitioned to the patient's home. During this period, the transition care and an advanced practice nurse (APN) will make regular house calls to conduct assessments, examine the patient and draw blood for laboratory studies, while the physician will be involved in the telecommunication with the patient. Laboratory tests are then run at the hospital and by mid-morning, the laboratory results will determine if the patient needs other interventions. If an acute event has occurred that cannot be managed safely at home — such as first evaluation of febrile neutropenia — the patient has to return to the hospital for further follow-up and care. Likewise, the patient may also return to the hospital for routine procedures, such as first blood transfusion to ensure that there are no reactions. Transplantation outcomes are monitored throughout the patient's care and a chart review is performed by the coordinator and specialist nurse to confirm the findings. The patient is then discharged back to

NUHS

National University Health System



The team at NCIS led by Prof Chng Wee Joo (pictured second from right).

the clinic following counts recovery. Our experiences with the first few patients have been encouraging. Apart from reduced outpatient load, patients are also spared from the tedious two-way trips to the hospital. Other intangible but no less important benefits include reducing the stressors on patients and caregivers and also allowing medical staff to build a closer bond with the patients and better identify with their needs through caring for them at home.

Future plans: What lies ahead...

Despite the encouraging pilot results, there remains a number of hurdles to overcome in order to increase the uptake of this novel model by patients. Firstly, there needs to be efforts to change the mindset amongst patients and caregivers, most of whom still believe that the hospital is the best place for treatment, despite increasing evidence to the contrary. Secondly, at a policy level, continuous concerted

efforts from NCIS leaders to engage MOH on healthcare financing for these new models of care are crucial to ensure that these programmes remain relevant in the years ahead. Only by resolving these challenges can the majority of patients be allowed to have their transplantations done in the comfort of their own homes. After all, as the adage goes - home is where the heart is.



Article by
Dr Michelle Poon
Senior Consultant
Department of Haematology-
Oncology, NCIS

Dr Michelle Poon has a special interest in lymphoproliferative disorders and hematopoietic stem cell transplantation. She underwent a one-year postdoctoral fellowship programme at the MD Anderson Cancer Center in the USA in 2012 to pursue this interest, especially in the use of hematopoietic transplantation and immunotherapy to treat lymphomas. Since her return, she has been actively involved in investigator initiated and pharmaceutical sponsored trials for lymphoproliferative disorders and hematopoietic transplantation. Her present research interests are in using novel clinical therapies for the management of patients with lymphoid malignancies (especially acute lymphoblastic leukaemia and lymphoma) as well as clinical haematopoietic stem cell transplantation for adults with haematological diseases. She has also published in several peer-reviewed journals and presented at regional and international meetings.

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1. Abid, M.B., et al., Safety and cost-effectiveness of outpatient autologous transplantation for multiple myeloma in Asia: single-center perspective from Singapore. *Bone Marrow Transplant*, 2017. 52(7): p. 1044-1046.
2. Ringdén, O., et al., Many days at home during neutropenia after allogeneic hematopoietic stem cell transplantation correlates with low incidence of acute graft-versus-host disease. *Biol Blood Marrow Transplant*, 2013. 19(2): p. 314-20.
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26 FEBRUARY 2019 COLLABORATION WITH CLINICAL RESEARCH MALAYSIA



Clinical Research Malaysia (CRM) signed a Memorandum of Understanding (MoU) with NUH to promote the development of clinical trials in the region. Through this partnership, CRM will work closely with specialists from NUH and NCIS in the training of clinicians with the knowledge and expertise in conducting early phase clinical trials. The initial focus of the collaboration will be in oncology clinical trials led by NCIS.

20 MARCH 2019 NCIS RIBBON CHALLENGE 2019



The second edition of the annual NCIS Ribbon Challenge was joined by approximately 750 members of the public. Participants enjoyed themselves at the educational cancer awareness carnival where they pinned a cancer ribbon each and wrote pledges to go for regular screening. More than 15,000 cancer ribbons were collected at the event! During the carnival, three cancer experts also shared insights on common cancers diagnosed in Singapore.

20 & 22 MARCH 2019 1ST CLINICAL TRIALS RESEARCH GROUP MASTERCLASS



The 1st Clinical Trials Research Group Masterclass was organised by our Clinical Trials Research Group. The two-day event invited speakers from various countries including the United States (Mayo Clinic and MD Anderson), Hong Kong (CUHK) and South Korea (Yonsei University). The workshop which was conducted to educate young oncologists on clinical trial protocol development, benefitted 19 participants from seven countries such as Japan, Korea, India, Hong Kong, Thailand, Malaysia and Singapore.

30 MARCH 2019 9TH NATIONAL MYELOMA PATIENT FORUM

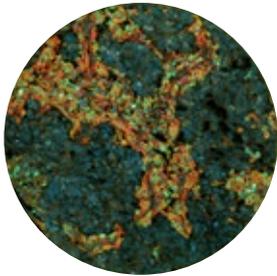


Jointly organised by NCIS and Tan Tock Seng Hospital, the 9th National Myeloma Patient Forum gathered more than 100 patients, caregivers and members of the public. Audiences heard from four myeloma experts who shared insights on a variety of interesting topics such as knowledge about myeloma and its treatment.

The Eternal Struggle for the Spotless Genome;

DNA REPAIR RESEARCH AT THE CSI

Deoxyribonucleic acid (DNA) is the heritable genetic material in our cells, and it carries information that encodes the building blocks of life. Our DNA is under constant attack from external and internal insults, ranging from cosmic rays and environmental pollutants to cellular metabolites that can modify DNA. To deal with this, our cells have evolved complex repair mechanisms that serve to protect the integrity of DNA.



Immune cells swarming around a tumour but unable to infiltrate it. Cytotoxic CD8+ T-cells (green), regulatory FOXP3+ T-cells (white), CD3+ T-cells (yellow) and CD163+ macrophages (orange), cell nuclei (blue).

When these repair mechanisms fail to function normally, DNA damage leads to the accumulation of genetic aberrations or mutations. Some of these can confer a selective growth advantage to the cell, ultimately leading to cancer. Accordingly, some forms of DNA repair abnormality are present in all cancers. Yet interestingly, DNA repair aberrations that lead to cancer development also serve as an Achilles

heel for tumours, allowing the therapeutic use of DNA damaging chemotherapy and radiotherapy in oncology.

Despite extensive research to improve our understanding of the cell biology of DNA repair pathways, this information is not used in routine clinical oncology practice when choosing therapeutic agents for individual patients. In my lab, we aim to translate the cell biological understanding of DNA repair to develop clinically applicable individualised onco-therapeutic options.

Specifically, we have 3 key areas of interest:

1. Development of microscopy assays to simultaneously study multiple proteins in cancer samples:

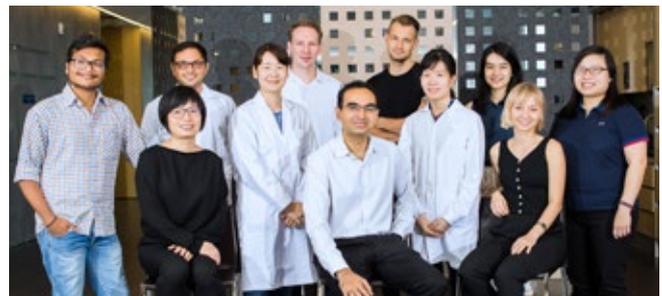
In routine pathological assessment, molecular markers are studied sequentially, which makes it difficult to understand their inter-relationships. So, to better understand the relationships between different DNA repair pathways in cells, we have developed a method called the multispectral microscopy which can simultaneously image multiple markers of interest. This is combined with machine learning algorithms to generate

quantitative data from clinical samples. We have used this method to identify patients who respond poorly to chemotherapy in B-cell lymphomas and ovarian cancer.

2. Understanding cancer associated abnormalities specifically in the homologous recombination (HR) DNA repair pathway: This pathway is lost in patients with mutations in BRCA1/2 and related genes, cancers with HR loss can be targeted by specific DNA repair inhibitors. We have discovered that certain cancers show an abnormal “hyperactivity” of the HR pathway which may make them resistant to such drugs and sensitive to others.

3. Enhancing immune recognition of cells with aberrant DNA repair: Damaged DNA is a potent stimulator of the immune system. We are working on methods to enhance the recognition of DNA damaged cancer cells by the immune system, specifically in the field of lymphoma. We collaborate with pharmaceutical companies to use test drugs targeting DNA repair to modulate immune recognition. Ultimately, we aim for this work to guide the design of clinical trials of DNA repair inhibitor, chemotherapy and immunotherapy combinations in lymphomas.

Science is a collective venture and we collaborate with clinical and scientific colleagues in Singapore and around the world to facilitate the above. Most importantly, the laboratory is an opportunity for me to work with wonderful PhD students (Michal and Allison), laboratory executives (Yanfen and Phuong) and post-doctoral fellows (Asia, Sai and Patrick) - my current co-explorers in this journey to understand and target the molecular basis of cancer.



Dr Anand (pictured seated in the middle) and his team at CSI.

Article by:

Dr Anand D Jeyasekharan

Principal Investigator
Cancer Science Institute of Singapore (CSI)

Consultant
Department of Haematology-Oncology, NCIS

Assistant Professor
Department of Medicine, Yong Loo Lin School of Medicine,
National University of Singapore (NUS)

Dr Anand Jeyasekharan joined the National University Hospital (NUH) in 2010 to complete his training in Internal Medicine, and Medical Oncology, after pursuing his PhD in Oncology at the University of Cambridge, UK. His laboratory at the CSI has been active since 2013, and focuses on understanding defects in DNA repair in tumours. He is a member of the NCIS lymphoma team, and has a special interest in high-grade B-cell malignancies.

HAEMATOLOGY SENIOR RESIDENCY PROGRAMME @ NCIS

Haematology is a unique specialty which requires clinical expertise as well as proficiency in laboratory medicine. This specialty is evolving rapidly, with new scientific discoveries having a major impact on patient outcomes. Haematology is hence one of the most challenging and exciting fields of medicine to practise.



At the Division of Haematology in NCIS, our mission is to train outstanding haematologists and inspire them to become leaders in patient care, education and research. The Haematology Senior Residency Programme was inaugurated in 2013 and our first senior resident Dr Joanne Lee graduated successfully in 2016. The training programme lasts 42 months with the first 24 months designed to fulfill the requirements of the ACGME-I. The last 18 months of the programme prepares the trainees towards the requirements of the Singapore Specialist Accreditation Board for Certification in Haematology. During this time, trainees will sit for the Fellowship of the Royal College of Pathologists (FRCPath) examination. We are pleased to announce that all the candidates from NUH who have sat the FRCPath examination in the 2019 spring session have passed.

Haematology training can be intensive yet rewarding at the same time. Trainees are expected to manage a heavy clinical workload coupled with laboratory reporting duties. The clinical service provides trainees with exposure to a broad range of patients including haematology-oncology, stem cell transplant and

benign haematology. In the laboratory, trainees have the opportunity to hone their skills in morphology, haemostasis and thrombosis, flow cytometry and transfusion medicine. The clinical haematology laboratory at NUH has a valuable collection of teaching materials which the trainees can use for their learning. Supported by a strong team, the lab also offers flow cytometry.

We provide a structured educational programme comprising weekly didactic sessions that cover all the major subspecialties within haematology. There are also learning opportunities at the multidisciplinary tumour boards and case discussions which take place weekly. Rotation to our participating site, Tan Tock Seng Hospital provides another valuable opportunity for trainees to further consolidate their skills, particularly in laboratory haematology.

At the research front, trainees are strongly encouraged to participate in research projects. Meetings with senior faculty dedicated to reviewing the progress of individual research projects occur on a regular basis. Many of our trainees have presented their work at local and international conferences and have published their research in renowned journals.

In the Haematology Senior Residency Programme at NCIS, we are proud of the achievements of our trainees and are confident that they will excel in their future careers.



Article by:

Dr Sanjay de Mel

Consultant

Division of Haematology, Department
of Haematology-Oncology, NCIS

Dr Sanjay de Mel is a consultant haematologist at NCIS. His clinical and research interests are in lymphoma and multiple myeloma. He is the programme director for the Haematology Senior Residency Programme at NCIS.

A Day in the Life of a HAEMATOLOGY RESIDENT



Can you describe a typical day at work?

My typical day at work involves leading ward rounds and teaching the junior residents. As most of the junior residents are new to haematology, it is important to teach and guide them during the ward rounds to help them understand the subspecialty better. For majority of the week, I conduct clinic consultations with my patients – sessions I enjoy and look forward to as I get to spend time interacting with them, understanding their problems and finding solutions to their medical conditions. During the laboratory posting, I will report the peripheral blood films and blood marrow reports at the lab. When encountered with challenging or interesting morphology cases, I will discuss with my consultants and present them in our weekly morphology rounds. On certain weeks, I also cover the procedure clinic where we perform bone marrow procedures and administer intrathecal chemotherapy treatments for our patients.

Was there any specific experience or patient that really affirmed your decision to work with cancer patients?

My decision to work with cancer patients is affirmed on a daily basis! Through interacting with my patients diagnosed with leukemia and lymphoma during my residency, I am constantly inspired by their strength and courage. Through deep conversations with my patients and their family members, they showed me what it means to persevere, to love, and to be determined to recover. Their strong will to live and lead a meaningful life reminds me of how precious time is, and how fortunate I am to have the opportunity to be their doctor, to treat and comfort them. They continue to motivate me to be a good doctor, and serve as a daily reminder of the purpose

and reason why I chose to be a clinician in the first place. My residency experience working with patients has also motivated me to want to further research on better treatment options, and to be involved in more projects which can help in improving my patients' quality of life.

What are some personal goals and dreams that you hope to achieve?

I hope to be able to look into more treatment options for the older population of haematology patients and focus on enhancing their quality of life. Management of elderly patients with haematological conditions is one area that we can improve on, to have a more holistic healthcare management to improve their life outcomes.

To improve patients' life outcomes, I will also like to study the possible ways to reduce patients' time spent in hospitals. This could include improving the cost effectiveness of treatment methods, as well as focusing on strengthening outpatient treatments, such as administration of chemotherapy. These will help our patients to have more time to be with their loved ones.

In addition, I will like to continue the education of haematology to the younger doctors, so that they have exposure to this subspecialty. I believe that once they understand the fulfilling nature of our job, they will be inspired to join us in the long run!

Dr Clarice Choong

Chief Resident (September 2018 to August 2019)

Department of Haematology-Oncology

National University Cancer Institute, Singapore (NCIS)

SPECIALIST AND TUMOUR GROUP LISTING

BLOOD CANCERS AND BLOOD DISORDERS

Bone Marrow and Stem Cell Transplant Programme

Haematology-Oncology

A/Prof Koh Liang Piu (Lead)
Dr Joanne Lee
Dr Michelle Poon
Dr Tan Lip Kun

Diagnostic Imaging

Dr Loi Hoi Yin

Radiation Oncology

Asst Prof Bala Vellayappan

Coagulation

Haematology-Oncology

Dr Chee Yen Lin (Lead)
Asst Prof Liu Te Chih
Dr Lee Shir Ying
Dr Yap Eng Soo

General Haematology

Haematology-Oncology

Dr Lee Shir Ying (Lead)
Asst Prof Liu Te Chih
Dr Cinnie Yentia Soekojo
Dr Clarice Choong
Dr Jen Wei Ying

Dr Joanne Lee

Dr Lee Chun Tsu

Dr Liu Pak Ling

Dr Ng Chin Hin

Dr Tan Lip Kun

Dr Winnie Teo

Dr Tung Moon Ley

Leukaemia, Myelodysplastic and Myeloproliferative Neoplasms (MDS/MPN)

Haematology-Oncology

Dr Ng Chin Hin (Lead)

A/Prof Koh Liang Piu

Dr Esther Chan

Dr Lui Pak Ling

Dr Melissa Ooi

Dr Tan Lip Kun

Dr Winnie Teo

Dr Tung Moon Ley

Diagnostic Imaging

Dr Loi Hoi Yin

Pathology

A/Prof Ng Siok Bian

A/Prof Tan Soo Yong

Radiation Oncology

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Lymphoma

Haematology-Oncology

Dr Michelle Poon (Lead)

Dr Esther Chan

Dr Chee Yen Lin

Dr Sanjay De Mel

Dr Anand D Jeyasekharan

Dr Joanne Lee

Dr Tan Lip Kun

Radiation Oncology

Asst Prof Wong Lea Choung

Asst Prof Bala Vellayappan

Dr Peh Wee Ming

Diagnostic Imaging

Asst Prof Arvind Kumar Sinha

Dr Loi Hoi Yin

Pathology

A/Prof Tan Soo Yong

A/Prof Ng Siok Bian

Dr Susan Hue

Dr Wang Shi

Multiple Myeloma

Haematology-Oncology

Prof Chng Wee Joo (Lead)

Dr Sanjay De Mel

Dr Melissa Ooi

Dr Cinnie Yentia Soekojo

Diagnostic Imaging

Asst Prof Arvind Kumar Sinha

Dr Loi Hoi Yin

Pathology

A/Prof Ng Siok Bian

A/Prof Tan Soo Yong

Radiation Oncology

Asst Prof Wong Lea Choung

Asst Prof Bala Vellayappan

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A/Prof Chou Ning

Dr Sein Lwin

Dr Vincent Nga

Dr Teo Kejia

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Dr Justin Christopher Ng

Dr Tan Ai Peng

Dr Jocelyn Wong

Dr Clement Yong

Haematology-Oncology

Dr Chong Wan Qin

Dr Andrea Wong

Paediatric Oncology

Dr Miriam Kimpo

Pathology

Dr Tan Char Loo

Radiation Oncology

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Asst Prof Bala Vellayappan

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A/Prof Mikael Hartman

A/Prof Philip Iau

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Dr Samuel Ow

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Asst Prof Vicky Koh

Dr Leong Yiat Horng

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Dr Yap Yan Lin

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Asst Prof Vicky Koh

Asst Prof Wong Lea Choung

Asst Prof Bala Vellayappan

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Dr Harish Mithiran Muthiah

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Asst Prof Koh Wee Yao

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Care Medicine

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A/Prof Lee Pyng

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Dr Khoo Kay Leong

Dr See Kay Choong

Dr Chan Hiang Ping

Dr Jeffrey Ng

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Microsurgery

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Asst Prof Arvind Kumar Sinha

Dr Sachin Agrawal

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Dr James Hallinan

Dr Salil Singbal

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Radiation Oncology

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Asst Prof Wong Lea Choung

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Paediatric Haematology-Oncology

A/Prof Quah Thuan Chong

Dr Miriam Kimpoo

Dr Bernice Oh

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A/Prof Quah Thuan Chong

A/Prof Tan Poh Lin

Dr Krista Francisco

Dr Miriam Kimpoo

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Plastic, Reconstructive &

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Surgical Oncology

A/Prof Thomas Loh

Dr Ng Li Shia

THYROID CANCER

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Dr Samantha Yang

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Surgical Oncology

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Dr Asim Shabbir

Diagnostic Imaging

Dr Sheldon Ng

Dr Prapul Rajendran

Dr Pavel Singh

Dr Yang Cunli

Gastroenterology &

Hepatology

Prof Lawrence Ho

A/Prof Yeoh Khay Guan

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Dr Raghav Sundar

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Pathology

A/Prof Nga Min En

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Dr Teh Ming

Dr Benjamin Wong

Radiation Oncology

Asst Prof Bala Vellayappan

Asst Prof Jeremy Tey

Asst Prof Francis Ho

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