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局部晚期非小細胞肺癌（NSCLC）

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【適應症】局部晚期非小細胞肺癌（NSCLC）IMFINZI適用於治療患有局部晚期、無法手術切除的非小細胞肺癌，且接受放射治療合併含鉑化療後病情未惡化的病人。【用法用量】IMFINZI的建議劑量為每公斤體重10毫克，靜脈輸注60分鐘，每兩週一次，直至疾病惡化或發生無法耐受的毒性為止。說明：連續使用本品一年以上的利益風險平衡尚未確認。【禁忌】無。【警語及注意事項】●免疫介導性肺炎，IMFINZI可能引起免疫介導性肺炎，其定義為需要使用皮質類固醇者。已有致死病例之報導。●免疫介導性結腸炎，IMFINZI可能引起免疫介導性結腸炎，其定義為需要使用皮質類固醇者。●免疫介導性肝炎，IMFINZI可能引起免疫介導性肝炎，其定義為需要使用皮質類固醇者。已有致死病例之報導。●免疫介導性內分泌病變，IMFINZI可能引起免疫介導性內分泌病變，包括甲狀腺疾病、腎上腺功能不全、第一型糖尿病和垂體炎/垂體低能症。●免疫介導性腎炎，IMFINZI可能引起免疫介導性腎炎，其定義為有腎功能不全的證據，需要使用皮質類固醇者。已出現致死病例。●免疫介導性皮膚反應，IMFINZI可能引起免疫介導性皮疹：使用本類藥物其他產品曾經發生大皰性皮炎（bullous dermatitis），史蒂文生－強生氏症候群（SJS）/毒性表皮溶解症（TEN）。●感染，IMFINZI可能引起嚴重的感染，包括致死病例。●輸注相關反應，IMFINZI可能引起嚴重或危及生命的輸液相關反應。【常見不良反應】最常見的不良反應（≥20%的病人發生）為咳嗽、疲勞、肺炎（pneumonitis）或放射性肺炎、上呼吸道感染、呼吸困難和皮疹。【使用前詳閱說明書警語及注意事項，詳細仿單資料備索】【僅限醫藥專業人員參考：處方藥物請參考衛生福利部核准仿單說明書】

Ref: 1. 衛福部核准仿單說明書 2. Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res.* 2015;3(9):1052-1062.

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暨臺北榮總60週年院慶學術討論會

1

精準醫學的最新進展

Recent Advances in Precision Medicine

時 間：108年6月22日 08:30~12:00

Time：June 22, 2019 08:30~12:00

地 點：台北國際會議中心 101A 會議室

Place：Conference Room 101A
Taipei International Convention Center

精準醫學的最新進展

Recent Advances in Precision Medicine

Experience of setting up a molecular diagnostic lab

建置分子實驗室經驗分享

Wen-Hui Ku

顧文輝

Taipei Institute of Pathology, Taipei, Taiwan, ROC

臺北病理中心

Pathology is the study of disease. In the past days, most of the pathological practices are making diagnoses by doing morphological researches. In the era of personalized medicine, the clinical role of pathologists now goes far beyond making diagnosis. The pathologists are increasingly involved in decisions on treatment and in monitoring of response to treatment, by using many molecular methods which are evolving rapidly.

Most of the molecular tests are highly complex, and the choice of which one to use depends on many factors. Timely and effective diagnosis is essential for many patients. Rapid and accurate diagnoses from small specimens in days is a key requirement. In order to provide adequate clinical services, as many clinical pathological Labs, a well-established quality management system is also necessary to molecular Labs. The experience in Taipei Institute of Pathology shows that how many factors should be considered and how many difficulties should be conquered in establishing a molecular lab.

Practical pipelines of whole exome and transcriptome sequencing for pathology research

病理研究之全外顯體與轉錄體定序的實用流程

Chin-Chen Pan

潘競成

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臺北榮民總醫院 病理檢驗部

Next generation sequencing technologies, such as whole exome sequencing and whole transcriptome sequencing, offer a high-throughput platform to investigate the genomics of diseases, including neoplasm. Herein we introduce practical pipelines for the analyses of genomic alterations from pathologist's perspective. General procedures, as well as tools and examples of detecting recurrent mutations, copy number variation, structural variations for DNA-seq, and detecting fusion, differential expression, gene set enrichment for RNA-seq, will be presented. We will use our published and ongoing studies, as well as the samples from TCGA repository for demonstration.

Clinical genomic profiling using the MSK-IMPACT™ to guide targeted and immune therapies

應用 MSK-IMPACT™ 平台進行臨床基因體檢測以引導標靶及免疫治療決策

Jin-Juan Yao

藥錦娟

Diagnostic Molecular Service, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

紀念斯隆 - 凱特琳癌症中心 病理部

MSK-IMPACT™ (Integrated Mutation Profiling of Actionable Cancer Targets) is a large panel NGS assay, targeting all the exons of 468 cancer related genes. It is the first academic tumor-profiling test to receive the US Food and Drug Administration (FDA) authorization for marketing.

MSK-IMPACT™ detects gene mutations and other critical genetic aberrations in both rare and common cancer types. Until now, genomic testing of tumors has been routine practice only for patients with certain solid tumors, such as melanoma, lung, and colon cancer. MSK-IMPACT™ is much more inclusive and can be used on any solid tumor regardless of its origin, potentially offering better treatment options to thousands of patients in the form of precision oncology, both targeted and immune therapies.

This presentation will illustrate the background of MSK-IMPACT™ testing, promising data from 40,000 clinical samples, and personalized patient management based on the MSK- IMPACT™ testing results. It will include the briefly introduction of the technology and work-flow of the assay, mutation annotation and the corresponding treatment options; then focus on the impressive findings of this universal sequencing effort, not only the somatic alterations of the tumors but also the discoveries in the normal control samples, such as germline predisposition and clonal hematopoiesis. The ultimate goal of this talk is to promote the utilization of large panel NGS clinical tumor profiling, to build the bridges between pathologists, oncologists and other related professionals in the joint endeavor of conquering tumors.

Clinical application of NGS for the management of advanced non-small cell lung cancer

次世代定序技術在非小細胞肺癌處置上的臨床應用

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蔡俊明[a] 童凱澤[b]

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[a] *臺北榮民總醫院 腫瘤醫學部*

[b] *行動基因生技股份有限公司 及 國立清華大學 生物資訊與結構生物研究所*

Nowadays, Precision medicine (select treatment for the patient, while not treat selected patient) plays an important role in patients with advanced non-small cell lung cancer (NSCLC). The targeted genes, EGFR, ALK, ROS1, BRAF, and NTRK, have become as a standard genetic test in NSCLC. As compared to the conventional genetic test, using multi-gene next-generation sequencing (NGS) technology is a more powerful and efficient approach that can identify hundreds of genetic information simultaneously. Here we share our clinical experience of using an appropriate size NGS test in treating our NSCLC patients.

The formalin-fixed, paraffin-embedded (FFPE) were collected from 100 patients with advanced NSCLC. 94 patients had received at least one treatment and six patients were treatment-naïve. The FFPE samples were profiled using a medium size NGS panel on the Ion Torrent system. The single nucleotide variants (SNV) and small InDels were detected in 35 or 40 genes, as well as copy number variations (CNVs) in 14 or 22 genes. The gene fusion status was evaluated by an RNA fusion test in 4 genes.

In total, the alternation of FDA-approved biomarkers was identified in 70.0% (70/100) patients. Other genetic alterations, including suggested biomarkers in NCCN guideline (ERBB2 mutations and CNVs, MET exon 14 alterations and RET fusions), and other potential actionable mutations (EGFR exon 20 insertions and CNVs, BRAF rare mutations, KRAS mutations and CNVs, ALK CNVs, MET CNVs, mTOR pathway, and cell cycle pathway alternation) were detected in 60.0% (60/100) patients. The co-occurred potential genomic alterations were discovered in 60.7% (37/61) of patients who had EGFR mutations at diagnosis. 78.3% (18/23) patients with post third generation EGFR TKI therapy had at least a co-occurring potentially actionable alterations with EGFR mutation. In patients with wild type EGFR and ALK or unknown-status at diagnosis, the targeted alternation was detected in 51.4% (19/37), and 21.6% (8/37) were FDA-approved biomarkers.

Our data suggest that using genetic test by a NGS panel at disease diagnosis or disease progression could identify more genetic alterations for targeted drug selection and guide the management for patients with advanced NSCLC.

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神而明之，存乎其人：神經學新知識

It is up to Every Individual to Try to Comprehend-New Knowledge of Neurology

時　間：108年6月22日　09:00~17:30
Time：June 22, 2019　09:00~17:30

地　點：台北國際會議中心 101B 會議室
Place：Conference Room 101B
Taipei International Convention Center

神而明之，存乎其人：神經學新知識

It is up to Every Individual to Try to Comprehend-New Knowledge of Neurology

Stereo-EEG: The route to the field of neuroscience

立體定位腦電波於神經科學之應用

Cheng-Chia Lee

李政家

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臺北榮民總醫院 神經外科

國立陽明大學 醫學院 及 腦科學研究中心

The effects of epilepsy are felt in multiple aspects of the person's life, including physical and mental health, cognitive function, educational achievements, vocational prospects, and family and peer relations. The successful treatment in patients with refractory epilepsy is the identification and localization of a potential surgical target.

In the past decades, intracranial EEG (iEEG), including subdural grid EEG and stereotactic EEG (sEEG), was used for precise EEG recording. Taipei Veterans General Hospital (TPE-VGH) is the only one center that can perform invasive presurgical evaluation of epilepsy using sEEG. Epilepsy surgery team in TPE-VGH have had the first case of sEEG implantation in 2014. The team also used data from SEEG to explore spreading of seizure activities in the patients with temporal lobe epilepsy, MR negative epilepsy, and epilepsy with migration disorders. The epilepsy surgery team provides good quality of presurgical evaluation and outstanding outcome of epilepsy surgery. In 2015, the team earned the award of "18th National Biotechnology and Medical Care Quality".

More recently, by collaborations with cognitive neuroscientists, several cognitive function including language functions were investigated based on the sEEG recording. Language about lexical tone processing in the brain is a good example. In Mandarin Chinese, there are four tones to distinguish word meaning. By comparing the intracranial EEG recorded under different task demands, the results indicated that EEG recordings from the frontal, temporal, and supramarginal electrodes showed differential responses to different cognitive demands. This is important because we can calculate correlation between electrodes from different brain areas to show how they work in concert to implement a cognitive function. We believe the sEEG is a route can take us on the route to the field of neuroscience.

Advances in reperfusion therapies from acute ischemic stroke to chronic carotid stenosis

從急性缺血中風到慢性頸動脈狹窄的再灌流治療最新進展

I-Hui Lee

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國立陽明大學 腦科學研究所

Endovascular therapy has emerged as an exciting treatment of patients with acute ischemic stroke. Acute ischemic infarction develops from the irreversible core to the areas of less severe hypoperfusion termed the penumbra. Timely reperfusion of cerebral blood flow above the threshold of penumbra is able to reverse functional deficits without permanent damage. Quantifying the mismatch between perfusion-weighted and diffusion-weighted imaging abnormalities serves as an indicator of the penumbra. In this talk, I will review the current guidelines of reperfusion therapies of intravenous thrombolysis and endovascular thrombectomy, discuss ischemia-reperfusion injury and potential mediators, and provide a roadmap for mismatch imaging-guided selection of patients particularly for late therapeutic window from 6 to 24 hours after stroke onset. On the other hand, revascularization therapy in asymptomatic patients with severe carotid stenosis is still being debated because of advances in optimal medical therapies. On this background, I will present our research on the long-term vascular and cognitive outcomes after carotid stenting compared to intensive medication alone in asymptomatic patients with severe carotid stenosis.

Strategical approaches to the cranio-vertebral junction

顱頸交界處的手術策略

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Diseases of the craniovertebral junction (CVJ) include degenerative, congenital, rheumatic, oncological, and trauma-related disorders. Surgical approaches to the CVJ has been challenging and can result in not only neurological deficits but also dysfunction of the upper aerodigestive tract. Therefore, the complexity of the surgical approaches has been long debated and attempted. Even with all the efforts made in years, however, few data are available regarding the incidence of complications after such surgery. Evaluation of a CVJ lesion for treatment must establish the biology, transverse and longitudinal extent of the lesion, and the preoperative and postoperative stability of the spine. Endoscopic approaches to the CVJ, which should reduce the expected morbidity of an open transoral approach, have been described recently. This lecture reviews common pathologies and various surgical approaches of the CVJ, and provides an evidence-based analysis of whether the endoscopic approaches reduce velopharyngeal insufficiency. Moreover, open surgery to the CVJ, including posterior, far lateral, and anterior lateral approaches, are thoroughly discussed. More than uncommon, after decompression, stabilization of the CVJ is sometimes mandatory for maintenance of neurological function. There are evolving technologies that aim to maximize the functional outcome of such disorders and will also be demonstrated. Strategical approaches to the CVJ aim to mitigate complications and increase neurological success of the complex surgery.

Headache medicine update in Taipei VGH

臺北榮民總醫院頭痛醫學最新進展

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國立陽明大學 腦科學研究中心

In this talk, I will report the advancement of headache medicine as well as the contributions done in our Neurology Department, Neurological Institute, Taipei Veterans General Hospital. In 2018, the International Headache Society published the 3rd edition of the diagnostic criteria, i.e. International Classification of Headache Disorders. In addition, the recent progress includes the neuroimaging, basic neuroscience and treatment, especially the discovery of the disease-associated neuropeptides such as CGRP and successful clinical trials of CGRP monoclonal antibodies in migraine patients. Most migraine patients only need acute abortive treatments, whereas preventive treatments are required for those with frequent attacks. In our hospital, we've focusing on the clinical research especially neuroimaging studies on certain headache disorders such as chronic migraine, reversible cerebral vasoconstriction syndrome, spontaneous intracranial hypotension and cluster headache.

Microneurosurgery at Taipei Veterans General Hospital: State of the art

最先進之神經外科顯微手術：臺北榮民總醫院經驗

Sanford PC Hsu

許秉權

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臺北榮民總醫院 神經外科

The modern microneurosurgery began with the pioneer work of professor M. Gazi Yasargil, Man of the Century 1950-2000, in 1967 when he developed the techniques and concepts of microneurosurgery in his routine operations in Zurich following his training in Burlington, USA. After his retirement in 1993, he was invited by professor Ossama Al-Mefty to join the neurosurgical department of the University of Arkansas for Medical Sciences in Little Rock, USA. During the following 15 years, Little Rock became the Mecca of neurosurgery in the world. Taipei Veterans General Hospital has had a good and strong connection between Little Rock ever since Dr. Sanford's fellowship at UAMS during 2007-2009. He conveyed the advanced techniques and concepts of microneurosurgery to Taiwan and transformed the outcomes of the patients with conditions that were previously considered inoperable. He established a multidisciplinary team including neurologists, ENT specialists, neurophysiologists to perform state-of-the art microsurgeries in routine practices of neuro-oncology, skull base and cerebrovascular diseases. He followed the steps of his mentors to begin and continue a series of microsurgical international courses per year in Taipei, which were recognized one of the best educational events by Aesculap Academy in Germany.

NCS/EMG: A clinical load or innovative work?

神經傳導 / 肌電圖：臨床負擔或創新工作？

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臺中榮民總醫院 神經醫學中心

Electrodiagnostic techniques are divided into two parts, nerve conduction studies (NCS) and electromyography (EMG). In the first part, we will discuss the routine NCS and how to translate them into scientific papers, mainly focused on electrodiagnosis of carpal tunnel syndrome (CTS). I will present an evidence-based and reasonable flowchart for the electrodiagnosis of CTS. CTS is a disease with compression of median nerve at wrist; however, a decrease of NCV occurs in 15-20% patients and the cause of reduction of CV remained uncertain. I will answer the queries: *exploring natural causes of decreased NCV in CTS: due to conduction blocking or slowing at wrist or retrograde axonal atrophy.*

CMAP amplitudes usually reflect sizes and numbers of motor units (size x number), and I will discuss how to use CMAP amplitudes to predict the needle, avoiding painful needle examination.

EMG findings: a) spontaneous activity: detecting unstable muscle membrane potentials, possibly occurring in inflammatory myopathy, acute denervation or status of chronic poor-reinnervation, b) motor units action potentials: polyphasia reflecting early loss with unstable morphology of motor units or chronic reinnervation with appearance of long duration or giant motor unit action potentials. I will discuss the indication of EMG in entrapment neuropathy, for example, in CTS and provide evidence on how to predict EMG findings based on CMAP amplitudes. Finally, I will talk on how to expand EMG in the field of treatment, for example, how to perform laryngeal EMG in the diagnosis of vocal cord palsy and how to use laryngeal EMG in the treatment of vocal cord palsy.

The history of Neurological Institute of Taipei Veterans General Hospital

神經醫學中心的沿革

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吳進安

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In 1959, when this hospital was established, the Department of Neurology was originally known as Division of Neuropsychiatry, which belongs to the Department of Medicine, leading by National Defense Medical Center Professor Xi-Gong Liu (劉錫恭) served as special physicians. Since 1963, Fu-Li Chu as the director of Division of Neuropsychiatry was the first neurologist in charge of Neuropsychiatry. Then, Department of Neuropsychiatry became an independent department in 1976, and further divided into two departments in 1983, the Department of Neurology and the Department of Psychiatry. The Department of Neurology comprised two divisions and two units, namely Division of General Neurology, Division of Cerebrovascular Diseases, Electromyogram (EMG) Lab and Electroencephalogram (EEG) Lab.

Integrating with Division of Neurosurgery, delicately planed by Director Fu-Li Chu and Director Liang-Shong Lee (李 良 雄), the Neurological Institute at Taipei Veterans General Hospital was founded in January 1989. This is the first institute consisted of specialists in neurological and neurosurgical disorders, and plays a leading role in Taiwan. The institute is composed of seven divisions, which are General Neurology, Cerebrovascular Diseases, Peripheral Nervous System Disorders, Epilepsy, General Neurosurgery, Pediatric Neurosurgery, Functional Neurosurgery, and one Neurological Intensive Care Unit (NCU). Moreover, Stroke Intensive Care Unit (SCU) was established in 1998. Four years later, Division of Neural Regeneration and Repair was founded in 2002. The NCU was renamed as Department of Neurological Intensive Care. Currently, the Neurological Institute is comprised of nine divisions and the SCU.

The voyage of a neurologist

神經科醫師迷航記：從專業到轉型的心路歷程

Ching-Piao Tsai
蔡清標
Taipei Beitou Health Management Hospital, Taipei, Taiwan, ROC
北投健康醫院

In 2013 after 33 years work in VGH, I made a big decision, although I was reluctant to leave this great umbrella. In 2013, I saw TSMC Morris Zhang, He founded TSMC at the age of 55. In 2013, when I was 58 years old, I could wait until 65-year-old to retire or leave VGH to do something, therefore, follow some Doctors, friends from financial sector and the real estate industry founded the Taipei Beitou Health Management Hospital in 2013.

It was the first week after leaving the big umbrella of VGH, because of the details of the establishment of the hospital were called back to the city council for reevaluation and criticized, the more the hospital stumbling, the more the hospital was growing, In 2014 to 2018, the performance has grown several times from the ugly duckling into a beautiful swan and now a company with an annual revenue of several hundred million. Although it's so difficult in the founding of the new hospital, it's still so happy to leave the VGH to touch the real so-called blue sky. The sky we used to realize was just only a small circle. I still feel sincerely thanks to VGH colleague. Without VGH's support Taipei Beitou Health Management Hospital would not be so successful because 90% of Beitou's physicians are from VGH.

"NP, PN, My feeling…"

「NP，PN，我的感……」

Ke Pei Kao
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As a 35-year-old and not completely successful member in Taipei Veterans General Hospital, I cherish the chance for transmitting something to young doctor in the 30 year anniversary of Institute of Neurology.

In this moment, Taiwan medical market faces the problems of market saturation, uneven distribution of resources, horizontal competition and pressure from research and performance. After the time of resident, attending physician and participating in the Veterans Affairs Council's project of reducing the gap between rural and urban areas, I became a teaching consultant of Taipei Medical University Hospital, a would-be medical center. In the era which artificially intelligence will replaces many of the functions of doctors, I want to briefly share my thoughts inspired by my experience.

At the disturbing time, Thomas Jefferson, one of establishers of America, said, "Dissent is the highest form of patriotism." My opinions are sincere and true while someone may consider them as dissent. When they are in elder age after few decades, I hope my dissent will help young doctors to answer the question, "What do I have without my profession?" Of course, I present my blessing to today's audience.

What I have learned as a neurologist

神經生涯教會我的事

Hsiu-Chih Liu

劉秀枝

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臺北榮民總醫院 神經內科

As a clinical neurologist, researcher and teacher for 32 years, I have witnessed the impact of computer science on advances of neuroscience, the growing fields of neurology and the increasing treatment options for neurological disorders. Electronic service such as electronic history, electronic imaging and e-journals not only significantly improved the clinical practice of patient caring but also sped up the sharing of important research findings. Even social media such as Facebook and LINE played an important role in the learning and advancement of scientific discoveries. As a freelance writer for magazine and newspaper column, I also served as a bridge between physicians and the general public by providing continued education of the general public on neurological diseases. Growing old and being retired for 12 years, I gradually realized that I might personally benefit from the advance of neurology, since the majority of neurological diseases, such as strokes and neurodegeneration, are age-related. Therefore, teaching and working with young, brilliant neurologists is not just an academic reward, it might also be a great feedback for one's health in later life.

Brain venous outflow impairment, cerebral blood flow dysregulation and dysfunction of neurovascular unit integrity in patients with cognitive impairment

腦靜脈回流 , 腦血流調節與神經血管單元結構完整及失智症

Han-Hwa Hu

胡漢華

Department of Neurology, Shuang-Ho Hospital, New Taipei City, Taiwan, ROC

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There are compelling evidences suggesting the association of vascular factors and dementia, and treatment of vascular risk factors will have a lower risk of developing AD in future, and incidence of dementia can be reduced by control of vascular factors. Thus, how vascular abnormalities interact with cognitive decline in the elderly has been one of the most important studies. Complex cerebral blood flow (CBF) regulation is operated through neurovascular units, including brain autoregulation (CA), vasomotor response and neurovascular coupling to ensure that the brain's blood supply is appropriately in need. From our preliminary data, we found the three mechanisms of CBF regulation are actually working in concert. With people in supine resting for 10 mins without any external stimulation and using transcranial Doppler (TCD) we can obtained many hemodynamic parameters and their trends, which reflect the various functions of CBF regulation of NVU, such as spontaneous fluctuation of blood flow velocity, pulsatility index (PI), cerebral vascular resistance (CVR), Mx, and many other parameters as well. Recently we have been developing a novel software for automatically analysis of all the above parameters, and normal values of these parameters may represent the structure integrity of neurovascular unit (SINU).

Recently, we accidently discover some interesting findings. For example, the profiles of jugular venous ultrasound of dementia patient was very similar to those of patients with transient global amnesia (TGA), which was noted to have abnormal brain venous return. We also found that venous outflow impairment, cerebral blood flow regulation and cerebrospinal fluid circulation are all related to each other. Besides, I will spend a few minutes to discuss the paradoxical vessel constriction during mental task in subjects with shift work. Because shift work (like a pilot) disrupts the alignment between circadian rhythms and the daily behavioral cycles and may cause cognitive impairment.

Deep brain stimulation (DBS) for movement disorders: Where we are?

深腦刺激術與運動障礙疾病之運用：現今發展

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Neuromodulation is technology that acts directly upon nervous system. It is the alteration or modulation of nerve activity by delivering electrical or pharmaceutical agents directly to a target area. The most established and widely used procedure for treatment of neurological disorders is deep brain stimulation (DBS). DBS is the practice of placing electrodes deep into the brain to stimulate subcortical structures with electrical current, has been increasing as a neurosurgical procedure for movement disorders over the past 20 years. Originally a treatment for essential tremor, then the applications of Parkinson's disease (PD) and dystonia were well investigated. The DBS technique has been further refined throughout the years by improved imaging techniques, advanced neurophysiological recording possibilities, and advances in hardware and software technology. DBS is now used across a wide spectrum of neurological and psychiatric disorders. In addition to applying electrical stimulation for clinical symptomatic relief, the electrodes implanted can also be used to record local electrical stimulation activity in the brain, making DBS a useful research tool. Human single-neuron recordings and local field potentials are now often recorded intraoperatively as electrodes are implanted. Thus, the increasing scope of DBS clinical applications is being matched by an increasing in investigational use, leading to a rapidly evolving understanding of cortical and subcortical neurocircuitry. Today, the lecture will introduce the development and evolution of DBS therapy for PD and discuss the clinical investigations, both in surgical technique and its possible mechanisms. Moreover, the role of intraoperative microelectrode recording in DBS surgery will be reviewed. Finally, the future of DBS in treatment of PD will be highlighted including the innovative hardware, surgical technique and more clinical applications in PD.

Technology and privacy

科技與隱私

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This is not a new issue, but it is a bigger challenge that we have to face in the era of rapid technological growth. We seem to be familiar and unfamiliar with this term. We want to enjoy the convenience of technology but worry about privacy invasion as well.

We enjoy the health improvement brought about by medical progress, but we also hope that personal privacy can be fully guaranteed. Biotechnology, information communication, and artificial intelligence are advancing by leaps and bounds. What balance points are more recognized by people? Back to the more familiar health care field, is there any good practice that can guarantee privacy to a certain extent without hindering the progress of medical research?

The traveling clouds

旅行的雲

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First of all, I would like to acknowledge Professor Jong-Ling Fuh in inviting me. Then I have to clarify that I'm here not because I am as outstanding as the other seniors and teachers, but because Professor Fuh wants to invite the middle age who does not work in Taipei Veterans General Hospital currently. The flowers will lose their colors without green leaves. Therefore, I will be the green leaves today.

Why this speech is titled "The traveling clouds"? According to the Bible, not Harrisson or NICP, Hebrews 12:1 (NIV), "For this reason, as we are circled by so great a cloud of witnesses, putting off every weight, and the sin into which we come so readily, let us keep on running in the way which is marked out for us," Since we have many pioneers who contribute to the field of Neurology, like the cloud of witnesses circling and guiding us, we should work hard and learn examples they have established. Next, please listen to what happened to my trip and what scenery I saw.

3

智慧醫療的應用

Application of Smart Healthcare

時 間：108年6月22日　　08:40~17:30

Time：June 22, 2019　　08:40~17:30

地 點：台北國際會議中心 三樓 宴會廳

Place：3 Floor, Conference Room Banquet Hall
Taipei International Convention Center

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智慧醫療的應用
Application of Smart Healthcare

The roadmap from smart hospital to the next-generation healthcare

從智慧醫院邁向次世代健康照護

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The Taipei Veterans General Hospital (TVGH) is committed to providing patient-centered and state-of-the-art medical services to 2.5 million outpatients and 120,000 inpatients every year. For the sake of quality, safety, and efficiency, TVGH has fully computerized its administrative and clinical services since 1990s. All patient's medical records are saved electronically, becoming a comprehensive data warehouse for population-based researches and precious resources in artificial intelligence era.

Following the introduction of information and communication technologies (ICTs) since 2010, TVGH has moved forward to being a "smart hospital" with two aims: first, to provide patient-centered and timely processes of care; and second, to improve quality and safety of medical care. Patients can find appropriate doctors for their discomforts using keyword searches and can make appointments and confirm scheduled tests using friendly apps on smart phones. There are interactive kiosks providing tour guide for outpatient environment in 8 different languages. Patients can also pay the bills either using apps or automatic transfer machines 24 hours a day. The waiting time for queuing has been 60% decrease and the approval rate was significantly improved above 90% in 2018.

The newly developed EMR provides timely alerts for drug-drug interactions and duplication of tests. All imaging and laboratory results over the past 10 years can be accessed online in seconds. After 2018, all study results and pharmacy information have been uploaded to the nationwide PharmCloud system. Therefore, the safety guard system can be extending to national database at the point of care. The quality and safety of care is significantly enhanced.

Looking forward to 2020s, the healthcare patterns shall be systemically reformed. Patients expect personalized, health-based, timely, proactive, and continuous care. On the other hand, hospitals' service volume and NHI budget is to be further constrained. The next-generation healthcare (NGH) is going to be an integration between cyber and physical healthcare environments. People, either healthy or sick, will be empowered to monitor and control their health status by advanced and user-friendly sensors and these health information will be collected by Internet of Things (IoT) and analyzed by on-line healthcare professionals. Only the risky or high-risky groups are to be advised for seeking medical services at the integrated healthcare providers, either primary care physicians or hospital-based specialists. All the personal medical records as well as personalized medical advices are delivered directly to each patient and, with authorization, to his/her family doctors for continuous care. In together with prestigious and international ICT industries, the TVGH is ready to providing such a NGH service to our citizens.

The impact of XR in medical education and clinical practice

延展實境科技創造優質的醫學教育及臨床照護

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Extended reality (XR) is the combination of digital and bio-reality experience through technology. Today's advances in technology can create augmented reality (AR) and virtual reality (VR), mixed reality (MR) soft and hard ware. With the XR tools, the users can bring digital objects to the physical world or bring physiological world objects to the digital world. XR Technology has applied these tools to education, training and medical care.

In addition to optimizing teaching content (beyond lecture, video, book, etc.), XR attracts trainees' attention and engagement, expect to reach goals of Miller's pyramid including Knows, Knows how, shows how, does. XR, as a simulation tool can achieve steps of Bloom's Taxonomy theory including remember, understand, apply, analyze, evaluate and create. Finally, OSCE is used to achieve the evaluation of Kirk Patrick's model. Overall, XR-based technology-enhanced education emphasized steps of discovery, integration, application (transfer), teaching and digital (practice) in the smart hospital.

The essence of medical education includes educating health caregivers and patients. In addition to video gaming, the use of XR in healthcare/education has increased significantly in recent years. Taipei Veteran General hospital (TVHG) innovated XR simulation Education area has a surreal design space. The XR and various vehicles can be integrated through information and cross-platform to inspire the creation of XR in this area. In addition to planning a series of lectures across the information technology community, the TVGH has created the first wave of bilingual XR material for education of trainees, health professionals, patients or families. The content including details of difference between tracheotomy and general intubation; home care for tracheotomy; soft bronchoscopy; oral cancer, early kidney cancer, atrial fibrillation, how to avoid needle sticks, and the correct classification of medical waste.

Current and future: A smart UDI system for medical devices management in the hospital

建置醫材單一識別系統智能化：現在與未來

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本系統採用醫材單一識別碼 (UDI)，廠商提供完整醫材 UDI 資料，補給室建置醫材院內碼與 UDI 條碼對應資料庫；資訊室配合各單位需求，規劃建置醫材庫儲及帳務管理的系統，自動帶入手術術式系統資料；醫護人員於執行手術中，確認欲植入特材項目，再利用條碼機讀取並帶入電子病歷 (護理紀錄)，系統自動傳簡訊及 e-mail 通知廠商補貨，並產出計價單，傳送計價費用組完成計價不漏帳；手術後，植入物特材條碼自動帶入手術紀錄。

目前，本院已將第三等級醫材納入招標規範，條碼資料庫比率達 100%，第一、二等級醫材，僅極少數無法提供條碼資料；本院醫材試用管理系統，自 108 年 1 月 1 日起，第一、二、三等級醫材，均須提供醫材 UDI 資料，方可進行新品試用。

本系統可直接擷取醫材條碼上傳健保署申報，並自動傳簡訊及 e-mail 通知廠商補貨，且結合手術紀錄，完整記錄病人使用醫材品項及數量；系統產出計價單，傳送費用計價組完成計價。

未來，研議手術醫材建置組套主碼，以組套計價，計價採線上作業；廠商逕於系統上處理訂單及結報作業；系統採連結健保局，及時更新系統資料，以避免溢收款項。

Transfusion safety and its effectiveness: A process reengineering work through information technology

資訊科技與流程再造：以輸血安全效益為例

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Radiotherapy is a complex procedure which needs seamless integration of many systems, such as medical records, simulation, radiation planning system, portal verification, and etc. To get full integration of different systems, we do several projects of office automation on our department ourselves instead of commercial products.

Electronic medical record of radiation oncology department is important to improve quality, save man-power, and speed daily practice. We have created an electronic patient data system of radiation oncology since 2004, which is based on Linux, database engine (PostgreSQL), and a web server (Apache). With the computerized tomography system in our department, a suitable computer system is needed to manage computerized images, such as simulation films, portal films and DRRs from RTP. A new 2D planning system is also done since there are no more real radiographic films and to avoid digitizing the blocks on simulation films.

Patient Data System was completed in 2004, and it has run well in daily practice till now. It helps physicians to spare time in medical data recording and provides summary information for clinical research. Portal Verification System simplifies daily portal verification, manages the simulation films, portal films and DRR from CT simulation altogether, and provides the potential of analyzing patient setup accuracy. Two dimension planning system provides an environment of computerized 2D planning system. It also configures MLC position on physician's workstation and physicians can modify it if necessary.

The office automation on radiation oncology department is an important and continuous process. The experience in Lo-Tung Pohai Hospital shows that the home-made systems are feasible and could be customized to special needs. Also it benefits in cost saving and the physicians' efficiency on medical process.

Using information technology and clinical data analysis to improve the quality of pressure injury care

運用資訊科技及臨床數據分析改善壓力性損傷之照護品質

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The incidence of pressure injury is the one of the important indicators of health care institutions around the world, also as a sensitive indicator to reflect the effectiveness of the structure, process and results of nursing care. The Joint Commission of Taiwan (JCT) included pressure injury incidence as an important quality indicator for clinical health care in 2011. According to a survey by the National Pressure Ulcer Advisory PPanel (NPUAP) in 2008, the incidence of pressure injury in acute wards is 0.4% to 38%, and the incidence of intensive care units is higher than 33%. According to Taiwan Clinical Performance Indicators (TCPI), the incidence of pressure injury in general wards was 0.108%, and that in medical intensive care units was 0.39% in medical centers in 2015. This data indicated that one patient occurred pressure injury in every 1,000 person-days in a general ward, and approximately four patients occurred per 1,000 person-days in the intensive care unit. Annual Report of Centers for Medicare & Medicaid Services (CMS) indicated pressure injury would increase medical costs, which showed that hospitalized patients with pressure injury consume USD 43,180 more than the patients without pressure injury in 2009. Therefore, reducing the incidence of pressure injury is the target goal of health care institutions.

We began with the systematic structural transformation in the nursing information system, introduced evidence-based pressure injury assessment and prediction tools, pressure injury classification, prevention care guidelines, and visualized educational training programs with pressure injury pictures. A systematic physical assessment of the new admitted patients through a structured assessment tool and conducts daily assessment of the pressure ulcer risk factors in Nursing Informative Systems by nursing staffs.

After analyzing the clinical data, the Nursing information System can intelligently pointed out the high-risk pressure injury population to the medical team members, and reminding to implement the evidence-based care strategies to prevent injury. Returned the clinical data to the care units every month to carry out various qualities improvement interventions. Multiple strategies by Nursing Informatics System and data analysis helped us to reduce the incidence and severity of pressure injury and promote clinical care quality.

A mobile solution for chemotherapy patient's safety: An application of artificial intelligence technology

運用智能輔助癌病化療給藥的智慧照護

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Intravenous infusion (IV) of anticancer drugs is a major treatment for cancer patients. If operated improperly, it can lead to great harm. Clinically, IV pump is commonly used to control infusion rate. And medication safety is ensured by double check by two nurses. However, such measures add burden to the heavy clinical work and cannot completely avoid human errors.

According to Emergency Care Research Institute (ECRI), among the top 10 medical technology hazards in 2013, "wrong administration dosage due to IV pump" ranked as high as the second place. IV pump is a separate device. If the nurse sets a wrong infusion rate, IV pump cannot sound any warning. To this end, we offer a mobile solution to chemotherapy patient. Smartphones are connected to "the chemotherapy administration system" and "the IV pump internal data system" for "system-to-system" data verification so as to reduce the risk of human errors.

This innovative chemotherapy administration solution contains smart man-machine verification and simplifies the procedures of double check by nurses. The system covers seven verification points, all of which must be completely correct before IV pump is initiated. In this way, the technological hazard of "wrong administration dosage due to IV pump" is successfully blocked.

Besides the mobile version, the chemotherapy administration system has a web version. The mobile-based man-machine verification is expanded to be applicable to the computer of mobile e-nursing cart. The hospital conducts over 6,000 cases of chemotherapy in average every month. This smart chemotherapy administration system can effectively ensure that the medication safety of chemotherapy patients and shorten the man-hour of nurses.

What's the impact of information system construction on the Big Data Center of the Taipei Veterans General Hospital?

臺北榮總大數據中心資訊系統

Yuan-Chia Chu, Chun-Hsing Lu, Chung-Yuan Lee

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Clinical Big data collection relies on the results of clinical trials and observational studies of administrative databases. However, these studies not only require many valuable resources but are usually time-consuming and cumbersome.

We try to build the infrastructure of the computer system called Big Data Center System (BDCS) at the Taipei Veterans General Hospital (VGH-TPE) in Taiwan. Multiple electronic healthcare databases are built into a Common Data Model (CDM) by applying the databases schema and coding book used in the Taiwan National health insurance research database (NHIRD) that maintains the anonymity and the confidentiality of each data containing sensitive information in a medical database.

BDCS was developed using a CDM, which transforms data from different sources into an NHIRD standardized format and facilities the implementation of standardized computer programs by automatically removing, generalizing, and expanding information. It is designed to enhance data privacy protection to a data warehouse and handle queries automatically.

We developed the infrastructure of the BDCS, including an integrated data warehouse and a surveillance workflow. BDCS supports a diverse range of analytic studies spanning from epidemiology, clinical decision-rule improvement, to electronic tool development. It is notable for three factors: (1) Simply removing all explicit identifiers before the release of the data is not enough to preserve the data confidentiality. (2) Including a diverse and large patients population. (3) Containing time series data including laboratory results.

The BDCS systems can integrate the workflow of cohort identification and CDM to accelerate the survey process of time-consuming and security engineering. Common data model and BDCS platform of VGH-TPE are built to advance the use and performance of healthcare data in improving patient care of artificial intelligence in medicine.

Roles of artificial intelligence in biomedical innovation

人工智慧在生醫創新的角色

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Artificial intelligence (AI), as the core of Industry 4.0, has substantially changed the industrial development and biomedical innovation is no exception. In computer science, the ultimate goal of AI is to create a computing system that is comparable or even superior to human in information communication and decision making that makes AI acts like or even better than human. However, the success in computer science is not necessarily equal to the success in biomedical science.

Nevertheless, AI is a powerful tool to facilitate and to accelerate biomedical innovation. Currently, the variety and diversity of biomedical data have made data analysis more difficult, in particular, the integrated multi-omics data combining with different forms of non-structural data strongly need AI to drive systematic data analysis.

Sarcopenia, a newly defined disease, is featured by the loss of skeletal muscle mass plus loss of muscle strength and/or physical performance. Until now, the diagnosis remained to be a challenge and the search for reliable biomarkers is under way. Using proteomic and metabolomics approaches, a great number of candidate biomarkers were selected, but unable to determine the most appropriate ones. Using machine learning, we successfully identified a candidate protein, named as Q7Z2, which was highly predictable for muscle mass, strength and walking speed. Q7Z2 has been cloned by cDNA but the function remained unknown. After serial experiments, the whole sequence and function of Q7Z2 become more and more clear and these novel findings will significantly improve the understanding of the pathophysiology of sarcopenia and the serve to be a reliable new biomarker for sarcopenia. Besides, deep learning also facilitates the identification of potentially new mediating pathways in the pathophysiology of parkinsonism and other neurodegenerative disorders.

In conclusion, AI is surely playing an essential role in the biomedical innovation beyond the success in computer sciences to simply develop an AI algorithm to approach physician's decision. Principles of AI in Industry 4.0 like automation and unmanned factory may not be all applied to health services because of the core of health care *per se*. Active using AI as the best instrument to create the biomedical innovation may be the best approach in scientific researches.

The clinical application of artificial intelligence in hemodialysis centers

智慧醫療在血液透析中心的應用

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Taiwan has the highest prevalence of end stage renal disease in the whole world. In addition, patients with end-stage renal disease suffered from multiple underlying comorbidities and several episodes of intradialysis complications. During the process of hemodialysis, to provide a framework for analyzing cardiovascular response to hemodialysis-induced hypovolemia, blood pressure change, heart rate variation and/or arterial and venous volume change are importance to provide high quality of dialysis therapy.

Recently, we have created Hemodialysis Electronic System in the hemodialysis centers at Taipei Veterans General Hospital, which is important to improve speed and quality, increase efficiency and productivity and emphasize personalized care and security. In our hemodialysis centers, the hemodialysis schedule for each patient is assigned automatically by the computer. The healthcare staffs are able to provide reliable and efficient care through the implementation of this robust quality hemodialysis management system and easy to assess patient health status and identification of high-risk patients for targeting for either preventative or therapeutic purposes. With the advancement of technology, we attempt to provide more reliable and efficient care in accordance with artificial intelligence. Artificial intelligence may be the proper tools for the prediction of the dialysis complications to guide the physicians to select proper management in improving dialysis outcomes. Establishment of artificial intelligence in our Hemodialysis Electronic System is benefiting enormously to predict the change of hemodialysis parameters, laboratory data and even the patient outcomes using statistics, algorithmics, machine learning, information retrieval, and data science. The success of use of such Hemodialysis Electronic Artificial Intelligence System allows the benefits to warn us in a timely manner with enough information to organize high-risk patients in the face of an impending disaster of hemodialysis change or life-threatening conditions.

Current and future trends for artificial intelligence in medicine: Development experiences in China Medical University Hospital

人工智慧醫療的現況與未來：中醫大發展經驗

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For today's speech, I am going to share my experience of using artificial intelligence in the field of clinical medicine. The establishment of a medical AI projects depend on plenty of clinical requirements from physicians. The initial assessment is to determine the feasibility of the project, and the discussion of pertinent details. After that, we proceed in data collection and data cleaning in order to build up a structural big database. This is the first stage, the process of data organization and acquisition.

The second stage involves model training. Through the use of the big database obtained from first stage, a deep-learning neural network model will be derived from this model training stage, and this is a vital part of this process. The clinical information department in the hospital provides an application programming interface (API) and the search criteria for the in-hospital database. After acquiring data, the interface will transfer them to neural network model for analysis, and a structural clinical research report will be finally obtained, which the results of the model analysis will be displayed through a web-page format.

AI provides a huge contribution to clinical medicine, and its future development is also unpredictable. It can not only enhance the accuracy rate of interpretation and shorten the operation time, but also reduce the potential burden of the clinical staff. In the future, the web-page research report could be adapted to a format for personal mobile devices, such as the chatbot system in some communication software, which will diversify the development of AI and the immediate service of healthcare.

Treatment of atrial fibrillation using deep learning in image data

以創新之心臟影像巨量資料治療心房顫動

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Arrhythmia is an important cause of sudden death and various complications in heart disease patients. Atrial fibrillation (AF) has a prevalence of up to 1% in the general population and an average increase in the rate of stroke more than five times. However, current drug and catheter ablation therapy have not yet reached the stage of completely eradicating AF, and there is a need to assist in clinical decision making through a variety of blossoming imaging tools. It is hoped that through the artificial intelligence (AI) model, a better tool than the traditional image feature analysis method can be developed to predict the prognosis of AF, the risk of stroke and death, to improve the treatment method, and the strategy of AF ablation. The most appropriate treatment for patients is the best personalized medicine.

Heart disease ranks among the top ten causes of death in Taiwan. In recent years, with the rapid development of various imaging examinations and catheter ablation treatments, the prognosis of patients has made considerable progress. However, with the increasing use of imaging inspections, the vast amount of data and the increasingly detailed classification of diseases have gradually exceeded the limits of the human brain. We applied the deep learning AI using pre-ablation computed tomography (CT) geometric slices to create the models for prediction of AF trigger and recurrence after catheter ablation in patients with AF. The website for assisting management of AF has been built. The auxiliary diagnosis website is divided into three parts. The first part is to input computed tomography scan to draw the left atrium; the second part is the input CT scan to calculate the freedom from recurrence of AF after catheter ablation, and use the hotspot map (GoogLeNet+GAP technique) to understand the location of the model; the third part is the use of CT image to help determine the location of the origin of AF, and understand whether the patient is a pulmonary vein triggered or non-PV triggered AF.

Smart wearables for cardiovascular diseases

穿戴性裝置於心血管疾病的創新發展

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The wearable devices as well as smartphone technology could monitor key physiological signals and provide useful information in the diagnosis and management of cardiovascular diseases. Devices, specifically designed to monitor heart rhythm and electrocardiographic signals, are useful for determining arrhythmias, such as atrial fibrillation. The recent advancement of artificial intelligence for signal process further increases the accuracy of diagnosis and speeds up the detection and management of arrhythmias. These new wearable and smartphone technologies have broken the barrier between patients and healthcare providers, leading to the real-time and patient-driven medical care. Several novel wearable technologies have been developed in our department accompanied by artificial intelligence-assisted diagnosis. We will update the recent progress and provide the insight for future clinical application and limitations.

Application of artificial intelligence in thoracolumbar spine fracture identification

人工智慧在脊椎胸腰椎骨折節判斷之運用

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Recent advances in artificial intelligence (AI) have shown great performance in identifying non-medical images, and the technology is thought to be the next technological revolution. So far some application regarding spine fractures identification in CT scan was investigated, and in this study we sought to determine the feasibility of using AI for thoracolumbar spine fracture identification in the skeletal radiographs.

After series of model testing, we used YOLO 3 model along with Xception to thoracolumbar fracture identification. Moreover, we tried to use U-Net model to segmentation, classify the severity of fracture and automatically calculation of spine deformity index (SDI). Unfortunately, the segmentation by the U-Net model did not work well. Some ambiguous identification of vertebral body might bias the segmentation results and make SDI calculation incorrect, especially segmentation in in the thoracic spines. We further tested other models in order to facilitate the IOU (intersection over union) when segmentation. The IOU approximately reach to 0.73 to 0.75 by the testing model.

If the AI model could work efficiently and precisely, the model might be helpful for non-orthopedic physicians who work in the first line in assisting the diagnosis and identification of vertebral thoracolumbar fractures in radiographs. It also benefits in time-saving for diagnosis and get the right treatment more efficiently for patients.

Can migraine attacks be predicted by electroencephalography (EEG)?

偏頭痛發作可否腦波預測？

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Migraine is a disabling headache disorder. Episodic migraine is considered a recurrent neurovascular headache with a cycle that includes four phases, i.e. inter-ictal, pre-ictal, ictal and post-ictal phases. The ictal phase is the period during which migraine patients suffer from headache; the pre-ictal phase is defined as 72 or 48 hours before the ictal phase, which is preceded by the inter-ictal phase. Electroencephalography (EEG) changes have been demonstrated before headache attacks, i.e. during the pre-ictal phase. In the past 5 years, we collaborated with National Chiao Tung University to use the EEGs signals to predict the migraine attacks. To predict migraine attacks is clinically useful because if acute treatment can be given earlier, the pain relief is usually more efficient. We measured the resting and steady state visual evoked potential (SSVEP) EEG changes in both migraine cross-sectionally and longitudinally as well as the healthy controls. For resting state, EEG band power and effective connectivity could be used to classify pre-ictal patients vs. inter-ictal phase. For resting EEG over the pre-frontal leads and SSVEP over occipital leads, inherent fuzzy entropy offers novel applications in both resting and visual stimulus environments and may have the potential to provide a pre-ictal alert to migraine patients. Overall, the classification accuracy is about 75 to 80% in our research, but needs validations in further studies on large-scale samples.

Digital pathology: An AI-assisted analysis system for neuroendocrine tumors

數位病理：神經內分泌腫瘤之數位影像輔助診斷系統

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梁文議

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Nearly one year after the FDA cleared the Philips IntelliSite Pathology Solution for primary diagnosis, there are getting more and more innovative pathology labs are working 100 percent with digital pathology for their current pathology workload. But large-scale adoption in the world may await a few remaining solutions and steps, among them next-generation scanning systems, improved viewing software, solid infrastructure, and an open versus a closed system approach. Full acceptance of the power of artificial intelligence could well be the biggest push of all.

In this section, we will introduce the applications of digital images in pathology practices, including teleconsultation, slides archives, tumor board discussing, quality control and education. Finally, will share our experience of using digital slides for primary diagnosis and AI-assisted diagnosis. We hope all attendant can find the best way and process to their future digital pathology practice.

Artificial intelligence in diabetic retinopathy

人工智慧影像判讀運用於糖尿病視網膜病變之現況發展

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Early detection of eye diseases is of great significance to prevent vision loss and promote living quality. Conventional diagnostic methods are tremendously depend on physicians' professional experience and knowledge, which consume manpower, cost, time, and material resources. Artificial intelligence (AI) has been widely applied to medical image recognition, including ophthalmology. AI has the potential to revolutionize current disease screening pattern and generate a significant clinical practice.

Deep learning system, one of the mainstream calculated module of AI in image analysis, has been used to analyze color fundus photography, optical coherence tomography, or visual field to achieve robust diagnostic performance in detecting diabetic retinopathy, retinopathy of prematurity, glaucoma-like disc, macular edema, and age-related macular degeneration. Deep learning has also been applied to telemedicine in screening, diagnostic, or monitoring eye diseases for patients in rural community. Disease screening and diagnosis need tremendous labour and financial support from health care systems. Therefore, AI may play very important role in screening disease or even providing treatment strategy in the near future.

The rapid growth in AI technology requires mutual understanding of not only technology but also clinical knowledge between physicians and computer scientists. In this review, I will briefly introduce current application in ophthalmic diseases, hope to provide comprehensive summary and facilitate promising AI projects in this field.

Establishment of AI-based e-cloud platform for diagnosing the retinopathy

開發雲端的黃斑部病變診斷服務

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Macula, one of the most important structures in human eyes, locates at the optical center of retina. Due to the complication of visual photo transduction pathway and distribution of cone and rod photoreceptors, a tiny change in macular may results in major disturbance of patient's vision. Among various ophthalmic exams for diagnosing macular diseases, optical coherence tomography (OCT) is one of the most important non-invasive tools. Based on the images captured by OCT, clinical ophthalmologists could understand the diagnoses, location, and activity of macular diseases.

Artificial intelligence (AI) has been widely applied to clinical territory to enhance medical workflow and improve health care quality. Plenty of research tried to improve and develop the assistance of clinical diagnosing process by training AI models to analyze and obtain clinical information from various medical image. Moreover, implementation of such AI-based software as an e-cloud platform for accomplishing telemedicine, the practice of providing medical care from a distance using electronic interfaces.

Herein, AI has been used to analyze the optical coherence tomography (OCT) image and then provide the recommendation to assist ophthalmologists diagnose retinal macular lesions and make decision for remedying those patient who suffer from age-related macular degeneration (AMD).

At present, the accuracy of our AI model was over 95%, which is higher than medical students and close to the specialists. The website has been established for realistic AI-based telemedicine which available at https://www.ym.edu.tw/~AI-OCT/. People can upload their OCT images to the website to verify whether they have AMD and require treatment. Using an AI-based cloud service represents a real solution for medical imaging diagnostics and telemedicine. Those achievements has been published in the journal of Theranostics.

Machine learning approach to phenotype psychiatric disorders using neuroimaging

透過機器學習以腦影像區分精神疾病

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The diagnostic systems in psychiatry have mostly relied on descriptive phenomenology that does not fully consider the heterogeneous symptoms or their biological mechanisms, etiology, and genotypes. This challenge is particularly true for psychotic disorders. We aim to develop the Research Domain Criteria (RDoC) strategy with machine learning-based computational algorithms to phenotype psychotic spectrum disorders.

This study included a cohort consists of 200 schizophrenic patients and 200 healthy Han Chinese retrieved from Taiwan Aging and Mental Illness (TAMI) cohort. Structural brain images in this cohort were acquired with a 3T magnetic resonance imaging (MRI) facility.

We have identified key regions of schizophrenia with the structural brain image. The key GM voxels identified by the EDNN were within brain regions including insula and precuneus. The machine learning achieved an average test accuracy of 92% in with matter, an average of 88% in grey matter and 75% in CSF.

We also construct a “diagnostic platform” to support decision making for the doctors in the clinic. The algorithms behind the platform have been validated. By inputting human brain image, the platform will present the output as a meaningful suggestion based on neuroimaging evidence that can serve as a diagnostic reference.

Set-ups of smart systems for neuro-rehabilitation

神經復健之智慧醫療系統的建立

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What is so-called “smart rehabilitation” or “intelligent medicine” After all, what makes rehabilitation smart? What element could be the critical point for leading our medical industry to next generation?

After many hard-workings in recent years, we have developed different systems for neurological disease including Stroke and Parkinson’s disease (PD). For clinical insights, patients with stroke show significant improvement compared to controls on Fugl-Meyer Assessment and Box and Block Test.

We also integrated new technology and wearing sensor to set up systems for PD in different therapeutic exercises.

In our opinion, smart rehabilitation should be including but not limited to following 6 elements: (1) advice from experts, (2) serious game, (3) sensors for users, (4) data requirement, (5) clinical execution, and (6) backend.

For first and second elements, to accomplish an interesting exercise making patients engaging and healthier, serious game is a fine solution. Professional advice from medical experts and practical skill from engineer should be fusion well by communication and respects. For third element, high-tech sensors are important tools to collect big data. For example, inertial measurement unit (IMU) is a very common and useful sensor to detect the movement of patients. For fourth element, collecting physiological data such as brain wave, physical quantities, motion track, and so on could help us find new indicators to better outcomes. And for clinical execution, training patients how to use new rehabilitation system is important. Clinician should be able to change exercise prescriptions for each persons. Finally, a stable backend plays a strong basis in the whole systems. However, the owner should be discussed by more experts.

In the future, the cycle of evolution goes on. We believe that with new technology and device to set up systems for neurorehabilitation would enrich the field of smart rehabilitation.

Application of smart interactive platform for balance disorders

智慧化互動式平台對於平衡功能疾患之應用

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Background: Patients with vestibular hypofunction frequently suffer from vertigo, nausea, postural instability and decreased balance performance, which often lead to fall accidents, causing severe disability. Vestibular hypofunction(VHF) causes many limitations in daily activities, such as housekeeping, shopping and walking. The neurological transmissions in vestibular systems degrade as people age would be a crucial reason for the deficit. Therefore, efficient evaluation tools for vestibular system is an essential dement for early detection and treatment for people with dizziness.

In our team, we have integrated previous experience of evaluations and training from hundreds of patients in clinic, and combine digital sensors for human motion capture and analysis. Then, we have designed many studies and test tools for patient with dizziness, falling, or vestibular hypofunction. Research findings: 1. we have successfully demonstrated in chronic vestibular hypofunction patients, the head-trunk-pelvis coordination during walking is decreased as compared with the age-matched healthy individuals. We have therefore developed specific exercise training programs for patients with VHF. 2. We have also established a multi-monitored gaze shift dynamic visual acuity (gsDVA) system. We found DVA and gsDVA performed during treadmill walking decreases in older population. The performance of GsDVA also decreases on the ipsilesional side of the VHF population. This 3-monitored gsDVA test is a more functionally relevant and more comfortable evaluation platform for patients with VHF. 3. The IMU attached on subjects head and torsa can detect head & trunk movements and DVA. This platform can compare the differences of head, trunk and pelvis movement range, velocity and reciprocal rotations between healthy individuals and vestibular hypofunction patients. Understanding the differences is the key of developing appropriate treatment plans.

Technical Achievements: 1. We honored the 14th National Innovated award in 2017. 2. According to the preliminary study, we established a walking DVA platform which can evaluate functional performance in healthy and diseased individuals during walking. Furthermore, we can establish a computer interactive and vestibular training program according the results. Patients with VHF can improve daily functional performance by this more functionally relevant training paradigm.

Utility of medical image AI in neonatal care: An investigation on necrotizing entercolitis of prematurity

醫學影像 AI 於新生兒照護之應用：以早產兒壞死性腸炎為例

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Necrotizing enterocolitis(NEC) is a life-threatening condition in infant, especially premature neonates. Supine abdominal x-rays are the mainstay of diagnosis. However, the radiographic features may be subtle in the very early stage of NEC, and the diagnostic performance depends on the interpreter. Convolutional network(CNN) is a widely-used deep learning technique for image pattern recognition and feature extraction. In this study, we used CNN model to predict risk of NEC by analyzing plain films.

We collected supine abdominal x-rays of neonates with age less than 1 month old (corrected age for preterm) in our NICU during 2016-2018. Chart review was done for analyzing NEC and feeding intolerance. A deep learning model based on convolutional neural network(CNN) was trained using prepared data aiming to predict severity of NEC and following feeding status. Gradient-weighted class activation mapping (Grad-CAM) was used to generate visualized explanation for decisions of the model.

We found that deep learning with CNN model on abdominal x-ray images revealed good performance for predicting feeding intolerance in high risk infant. By analyzing plain films using CNN models, clinical alert of NEC may be make automatically.

Augmented intelligence to the interpretation of chest radiograph

胸部 X 光影像之人工智慧輔助判讀

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Chest radiography (CXR) remains the most readily available imaging modality to screen various thoracic diseases worldwide. The interpretations of CXR were always a challenge for most of the physicians.

This retrospective cohort study enrolled preoperative and pre-biopsy CXRs of 595 patients at Taipei Veterans General Hospital from January 2007 to June 2017. Based on the pathology results, the findings were classified into benign and malignant groups with 176 and 419 cases. The pathology stages of all patients in the malignant group were T1-2NxM0. The mean age and the numbers of male and female were 64, 319 (53.6%), and 276 (46.4%). The NIH chest X-ray dataset composed of 27237 PA and 3568 AP views was mainly regarded as validation data. We adopted two types of AI methods to develop an application system for assisting the interpretation of CXR. The first method comprised medical image analysis and machine learning to differentiate the malignant from the benign opacity. The second method identified patient sex and the projection of AP and PA by using deep learning.

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the application system in identifying malignant opacity were 82.3% (345/419), 84.7% (149/176), 92.7% (345/372), 66.8% (149/223), and 83.0% (494/595). The areas under the receiver operating characteristic curve in differentiating the patient sex and the projection were 0.976 and 0.99, respectively.

This study exhibits the ability of AI to assist in the interpretation of CXR. Further prospective validation of this model within the clinical setting is warranted.

Toward artificial intelligence by medical images

運用醫學影像發展人工智慧

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With the thriving of deep learning techniques and high-speed graphics processing units, recent years have witnessed the beginning of a golden era of image analysis. Practicing smart healthcare and using machine learning techniques to segment, track and classify diseases in medical images, thereby relieving clinicians from the heavy burden of image diagnosis and improving healthcare quality, have evolved into a global trend. In particular, rapidly growing deep learning techniques such as transfer learning, YOLO, and U-Net may be combined with traditional machine learning methods and applied to medical images at varied data volume levels to broaden the spectrum of diagnostic techniques for medical images. This talk discusses clinical examples to explain how important machine learning techniques can be integrated with clinical medical data and professional clinicians' accumulated experience. In the long run, the developments of machine learning techniques to medical image analysis and diagnosis methods are expected to enhance the establishment of real time, accurate, and comprehensive diagnoses to assist medical experts for clinical practice.

AI-assisted outpatient clinic service at Taipei Veterans General Hospital

臺北榮民總醫院的人工智慧輔助門診

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Nowadays, almost none of us is exempted from the impact of artificial intelligence (AI). Medical community is just the one among many others that face this ever-revolutionary challenge in human being history. Our hospital (Taipei Veterans General Hospital, VGHTPE) starts to explore the application of AI in medicine not early. However, with the hospital investment in digitalization since early 2000's, we have collected the longest and largest longitudinal digital medical records in the country. This hospital investment with envision brought us unique situation to develop imaging AI in this revolutionary era.

We inferenced an AI model for brain tumor detection, namely DeepMets® (developed by VGHTPE and Taiwan AI Labs), into clinical scenario on November 17, 2018. On January 19, 2019 we went steps further and launched three imaging AI models of neuroimaging, cardiology and orthopedics (developed by VGHTPE and National Chiao-Tung University) and DeepMets® to our out-patient clinic. The launch has been a "never-before" in Taiwan and seen as an indicator of "Down-to-ground" and "Grass-root". In the last few months, we have shown the feasibility of having AI to assist physicians in imaging diagnosis, shortening lengthy clinical process, improving working environment and service quality. As a result, it is also found that AI-assistance facilitates our interaction with patients and allows us to "see" and "talk" more to them.

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膽胰管內視鏡治療之新進展

Advances in Therapeutic ERCP

主辦單位：中華醫學會
協辦單位：台灣消化系醫學會、台灣消化系內視鏡醫學會、
台灣肝臟研究學會、臺灣肝癌醫學會

時 間：108年6月22日 08:25~12:00
Time：June 22, 2019 08:25~12:00

地 點：台北國際會議中心 101D 會議室
Place：Conference Room 101D
Taipei International Convention Center

膽胰管內視鏡治療之新進展
Advances in Therapeutic ERCP

ERCP-directed radiofrequency ablation

經膽胰管內視鏡之熱射頻消融術

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Currently, the standard therapy for inoperable malignant biliary obstruction is stenting. However, the high occlusion rates were noted in metal or plastic stent. To solve this problem, endoscopically delivered photodynamic therapy (PDT) was developed. Although PDT improves survival and biliary patency, its high cost and phototoxicity limit its application. Steel et al. first reported that the efficacy and safety of endoscopically applied radiofrequency ablation (RFA) in malignant biliary obstruction. Strand et al. further demonstrated that biliary RFA had comparable outcome to PDT. To date, several additional case series have investigated the use of endoscopic biliary RFA for the treatment of malignant biliary strictures. It has been suggested that biliary RFA may increase SEMS patency and potentially improve survival, A meta-analysis by Zheng et al. including nine studies comprising 263 patients showed that a significant increase in stricture diameter and survival time by RFA treatment; however, the pooled rate of adverse events was 17% and three death occurred due to hemobilia and liver infarction. In addition, the cases of the enrolled studies are relatively small and the tumor conditions, RFA settings and types of biliary stents are variable. Hence, although intraductal endoscopic RFA holds promise in treatment of malignant biliary strictures, prospective randomized trials are needed to validate its effect.

Balloon dilatation time in EPBD

十二指腸乳頭氣球擴張術之擴張時間

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Endoscopic papillary balloon dilation (EPBD) is an alternative to endoscopic sphincterotomy (EST) for removing bile duct stones. EPBD has several advantages over EST, including a lower risk of bleeding, preservation of the function of sphincter of Oddi, and technical ease in altered or difficult anatomy. Given the lower risk of bleeding and recurrent bile duct stones, the European Society of Gastrointestinal Endoscopy (ESGE) guideline suggests EPBD as an alternative to EST for removal of bile duct stones, especially in patients with coagulopathy or altered anatomy.

A short dilation duration (≦ 1 minute) was previously recommended to reduce risk of pancreatitis after EPBD, but recent evidence indicates the opposite and supports using a longer dilation duration of around 5 minutes. A randomized controlled trial (RCT) found that EPBD with 5 minutes duration had a lower risk of pancreatitis (4.8% vs 15.1%, p=0.038) and failed stone extraction (7.1% vs 19.8%, p=0.024) than EPBD with 1-minute duration. Meta-analysis of previous trials showed that EPBD for less than 1 minute had a higher risk for pancreatitis than EST (odds ratio [OR] 4.14 [95% credible interval, 1.58–12.56]), whereas EPBD for longer duration did not pose a higher risk (OR 1.07, 95% credible interval 0.38–2.76); every 1-minute increase in dilation duration up to 5 minutes was associated with a 45.1% reduction in the relative risk of pancreatitis. Therefore, an adequate dilation duration, preferably 5 minutes, is recommended for EPBD.

Compared with EST, EPBD preserves biliary sphincter function and thereby approximately halves long-term risk of recurrent choledocholithiasis. In a prospective follow-up study of patients randomized to either 1 or 5 minutes of EPBD for choledocholithiasis, there was no significant difference between the groups in the risk of recurrent choledocholithiasis, cholangitis, and hepatobiliary complications. Those results support that a longer dilation does not cause a greater loss in sphincter destruction and higher risk of recurrent stones compared with a short dilation duration. Collectively, EPBD with adequate duration has a similar pancreatitis risk and a lower overall complication rate compared with EST for choledocholithiasis. A longer dilation duration during EPBD optimizes short-term outcomes without obviating the long-term benefits of EPBD over EST.

Therapeutic ERCP in post-liver transplant biliary complications

膽胰管內視鏡在肝移植術後膽道併發症之治療

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The main biliary complications after liver transplantation are bile leakage and bile duct stricture. The two complications can coexist. Their incidences are higher in living donor liver transplantation (LDLT), which is more complicated due to the involvement of hilum. How to make a correct diagnosis is the first problem to face. Choices of therapeutic modalities depend on the nature of the biliary complications and available facilities in each medical institution. Endoscopic therapy complemented with either radiologically-guided or surgical intervention is the standard of care. When managing bile leakage, adequate percutaneous drainage of bilioma before internal biliary stenting provides a better outcome; while balloon dilation with multiple plastic stents is the main choice of therapy for bile duct stricture in LDLT. Several rescue modalities are employed to deal with difficult clinical scenario recently, which include rendezvous procedure, Yamanouchi magnetic compression anastomosis (YMCA) or Spyglass choledochoscopy. In the condition of partial IHD dilation, it is weird in the clinical course. Treatment or not is also controversial. Is the intra-ductal metallic stent will be the first choice in the treatment of bile duct stricture of LDLT in the future? At present, endoscopic based treatment plays the key role in the treatment of biliary complications after liver transplantation.

Spyglass: Update

直視膽道內視鏡 (SpyGlass) 的新進展

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The biliary tree is among the most elusory structures for endoscopic examination. Cholangioscopy allows direct visualization and subsequent therapeutic maneuvers of the pancreato-biliary duct system. With advances in endoscopic and imaging technology, Spyglass cholangioscopy has become an important modality for the diagnosis of indeterminate biliary strictures and an essential therapeutic tool for difficult to remove pancreato-biliary stones. Enhanced imaging and operability of the latest generation Spyglass have further expanded their clinical applications including access to difficult to reach branches of the biliary tree, gallbladder drainage, biliary foreign body manipulation, and used together with ductal tumor radiofrequency ablation (RFA) or probe-based confocal laser endomicroscopy (pCLE). In this topic, we will discuss the technical evolution of cholangioscopy into the digital era and review the clinical evidence supporting its use in the diagnosis and management of pancreato-biliary tract diseases.

Biliary stenting of hilar tumour

膽道支架置放在肝門腫瘤病患的應用

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In the context of hilar cholangiocarcinoma (HCCA) that is surgically resectable, pre-operative biliary drainage (PBD) may be required for relief of symptoms or optimization of functional status prior to surgery. It should, however, not be performed routinely due to concerns of post-procedure complications. In the context of patients where curative resection is not possible, drainage is needed for palliation of symptoms. Options include surgical bypass, percutaneous drainage and endoscopic drainage. Non-surgical drainage is preferred as it is less invasive. Prior to drainage, the anatomy of the stricture and the sites of drainage should be defined by MRCP. The aim is to drain more than 50% of the liver volume. For patients with life expectancy longer than 3 months, metallic stents are preferred over plastic stents due to longer stent patency. A single stent is sufficient for Bismuth-Corlette type I HCCA. In the case of Bismuth-Corlette type II HCCA, ERCP with either unilateral or bilateral stenting is performed, depending on whether a single stent is sufficient to drain more than 50% of the liver volume. When bilateral metallic stenting is required during endoscopic drainage, this can be achieved by either the side-by-side or stent-in-stent methods. In the case of Bismuth-Corlette type III/ IV HCCA, the percutaneous approach is preferred over the endoscopic approach and depending on whether more 50% of the liver volume can be drained adequately by a single stent, bilateral or multi-segmental stenting may be required. Internal placement of metal stents is preferred over external catheter drainage or internal plastic stenting for the palliation of jaundice and should be performed when feasible.

Endoscopic ultrasound-guided biliary drainage (EUS-BD)

內視鏡超音波導引膽管引流之操作及應用

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Transpapillary drainage is the treatment of choice for obstructive jaundice. However, because of various reasons, the transpapillary approach can be difficult on some occasions. EUS-guided biliary drainage (EUS-BD) was developed to achieve successful drainage in such cases. EUS-BD is classified into the following four types: EUS-guided choledochoduodenostomy (EUS-CDS); EUS-guided hepaticogastrostomy (EUS-HGS); 3) rendezvous method, whereby the bile duct is punctured transgastrointestinally, a guidewire is advanced in an antegrade manner and then pulled out from the papilla, and, using this guidewire, the transpapillary approach is performed to reach the bile duct; and 4) antegrade method, in which the intrahepatic bile duct is punctured transgastrically and, using this route, a stent is placed in an antegrade manner.

Available data show a high success rate and acceptable adverse event rate for EUS-BD. Outcomes of EUS-BD appear equivalent to percutaneous drainage and ERCP. A successful EUS-BD procedure involves many technical steps, including puncture of the target site, needle exchange, and one or two attempts at tract dilation and stenting procedures. For a successful procedure, each step should be successful. If the procedure fails after tract dilation, it may lead to serious complications. Dedicated accessories and devices including specialized stents should be developed to maximize the efficiency while minimizing adverse events.

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精準醫療於遺傳性疾病

Precision Medicine in Genetic Disease

時 間：108年6月22日　　08:30~17:30

Time：June 22, 2019　　08:30~17:30

地 點：台北國際會議中心 102 會議室

Place：Conference Room 102
Taipei International Convention Center

精準醫療於遺傳性疾病
Precision Medicine in Genetic Disease

Current studies of Fabry Disease in Taiwan

臺灣法布瑞氏症的研究現況

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Since January 2008, our team has started the newborn screening of Fabry disease in Taiwan. Until Dec. 2018, total of 1,245,744, newborns have been screened. The incidence of Fabry mutation in male infant is 1/1,397. More than 2,100 individuals carrying Fabry (GLA) mutation were identified at our center. Around 84% (1,747) of them are caused by a specific mutation, IVS4+919G > A. The prevalence of left ventricular hypertrophy (LVH) occurred in 67% of males and 32% of females over 40 years old.

Previous studies revealed that to achieve long-term improvement in myocardial morphology and function, enzyme replacement therapy (ERT) should best be started before myocardial fibrosis has developed. However, our current study revealed significant cardiomyocyte substrate accumulation in IVS4 patients led to severe and irreversible cardiac fibrosis could occur before development of LVH or other significant cardiac manifestations. Furthermore, via Gb3 immunostaining study, our team identified significant Gb3 accumulation in cardiomyocytes before the development of typical histopathologic findings of Fabry disease. These findings indicate that Gb3 accumulation in cardiomyocytes and cardiac damages could occur much earlier than our previous expectation. The genotyping study of IVS4 patients was performed by llumina Infinium CoreExome-24 microarray. A common haplotype of the all studied 33 IVS4 males was identified and suggested this mutation was caused by a founder effect. Regarding studies of gene therapy, we tried to use AAV8, AVV9 and Anc80 to treat G3Stg/GLAko mice and demonstrated the therapeutic potential of AAV vector–mediated GLA gene therapy for Fabry disease.

Screening, diagnosis, and management of patients with Fabry Disease

法布瑞氏症的篩檢、診斷與處置

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Patients with Fabry disease (FD) are at a high risk for developing chronic kidney disease and cardiovascular disease. The availability of specific but costly therapy has elevated the profile of this rare condition. Though this disease is X-linked, both males and females are affected by it.

The diagnosis is established in males by alfa-galactosidase A–specific activity that is below 25% to 30% of mean control in peripheral white blood cells. Alpha-galactosidase A activity is somewhat predictive of classic or later-onset manifestations. Classically affected hemizygotes have undetectable or very low (£3%) enzymatic activity. As with many genetic diseases, there is a wide phenotypic variability even among patients with the same GLA mutation. In heterozygous females, random X-inactivation may result in expression of alfa-galactosidase A activity in the plasma or leucocytes within the normal range in up to 60% of women. Sequencing of the GLA gene is necessary for a diagnosis of FD in most females. The finding of elevated globotriaosylceramide (Gb3) in relevant tissues should be the ultimate requirement when confronted with GLA variants of unknown significance

Based on recent newborn screening studies each including at least 30,000 newborns, the prevalence of FD was found to be markedly higher than previously expected with 1 in 3100 males reported in northwestern Italy, 1 in 3000 males in Austria, 1 in 1300 males in Taiwan. High-risk screening: Screening for stroke in the young has shown definite FD in 0.5%, in 0.9% of the hypertensive population with left ventricular hypertrophy, in 0.5% to 1% of patients with idiopathic hypertrophic cardiomyopathy but 4% of males, and in 0.11% to 0.17% of dialysis patients. The X-linked nature of FD inheritance renders cascade screening of families efficient and of high diagnostic yield over on average 3 generations surrounding an index case.

ERT with recombinant human alfa-galactosidase A (agalsidase) is the only currently available therapy aimed at the etiology of FD, and suitable for all pathogenic mutations. Agalsidase-alfa and agalsidase-beta have been studied in clinical trials with different primary end points, hampering comparison of effectiveness. There is no scientific evidence as to the optimal age of ERT initiation. Therefore, there are no uniform guidelines, and conditions and age to start ERT differ in various countries. The benefits of early treatment, before irreversible tissue injury occurs, should be balanced against the burden of biweekly infusions in very young individuals.

FD is a complex multisystem disease with mostly nonspecific symptoms and signs. Diagnosis requires a high index of suspicion in symptomatic patients and screening of certain at-risk groups. Common standard-of-care therapies are highly effective in alleviating symptoms and treating disease com-plications. ERT is the first specific therapy developed that can slow kidney disease and alleviate symptoms but confers little benefit to cardiovascular and cerebrovascular outcomes.

Effectiveness of enzyme replacement in cardiac outcomes of Fabry Disease

酵素補充治療在法布瑞氏症心臟變異型的治療療效

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The majority of patients suffering from (Anderson-) Fabry's Disease are dying because of cardiovascular complications. Cardiac and cardiovascular manifestations are notable from early childhood starting at least in the classical phenotypes with a cardioneuropathy and concentric remodeling and chronotropic incompetence, ending with severe hypertrophic cardiomyopathy with myocardial fibrosis. Symptoms of decompensation as arrhythmias, fatigue, dyspnoe, chest angina pain arise in the late twenties in males and around the late thirties in females.

Since 2001 different enzyme substitution strategies and nowadays a chaperone therapy are available for treatment of Fabry's disease. Long-term treatment results are indicating, that early initiation of enzyme replacement therapy is able to prevent early severe organ involvement, while later treatment in advanced stages of the disease will result in a slowing down of the progression rate of the fatal complications of the disease. In regard to the heart, it can be shown, that treatment with agalsidase alfa over 10 years are related to an improve in clinical signs and symptoms as indicated by an improvement in NYHA functional class and CCS class for chest angina pain. Results for both enzyme replacement therapies and for the chaperone therapy will be presented and discussed.

Outcomes of very early treated infantile Pompe Disease: 10-experience of Taiwan newborn screening program

非常早期治療之新生兒型龐貝氏症預後分析：台灣新生兒篩檢之 10 年經驗

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Background: Pompe disease is an autosomal-recessive lysosomal storage disorder characterized by the deficiency of acid a-glucosidase(GAA) which leads to the progressive accumulation of glycogen in numerous types of cells and tissues. A broad spectrum is observed, ranging from the severe, rapidly progressive infantile-onset Pompe disease (IOPD) to late-onset Pompe disease (LOPD). Early enzyme-replacement therapy (ERT) can prolong survival and improve the long-term outcome of Pompe patients. Taipei Veterans General Hospital (TVGH) began Pompe newborn screening from 2008. Until now, we had tested approximately 1.2 million newborns. By 2010, we established effective, rapid diagnostic strategies. With such an effective system, our patients with IOPD started their ERT younger than 10 days of age. In this 10-year cohort study, we reported the prognosis of 25 IOPD patients who received very early ERT.

Method: From 2008, more than 1.2 million newborns were included in our series. Twenty-five IOPD patients were diagnosed and treated in our center. Long-term surveys of biomarkers, echocardiography, physical and mental development, articulation assessment, respiratory function and brain MRI for CNS involvement were performed. We analyzed the data between our patients, especially who carried the identical mutation (c.1935 C>A, homozygous) and also compared to other study groups.

Results: The age at first ERT of our IOPD patients was around 9.7-day-old. Our patients had lowest IgG antibody level, the average was 1:400. They all had normal body weight and body height, according to the age. None of them needed invasive mechanical ventilators and no one needed walking devices. However, we found most of them have in various degrees of anatomic upper airway abnormalities and articulation disorders, even receiving very early and regular ERT. Two of them needed night-time NIPPV and most of

them needed to receive language therapy. Moreover, five of they showed mild CNS involvement but no cognitive abnormalities were noted.

Conclusion: We presented the 10-year outcome of very early treated IOPD patients in this study. The results showed that early treatment was the critical factor for the prognosis of Pompe disease. However, we found the insufficiency of respiratory function and the power of buccal muscle in our patients who have already started ERT shortly after birth. Long-term effect of current treatment for Pompe disease was needed to be observed persistently and next-generation therapies were expected to provide the better outcome of Pompe disease.

Diagnostic odyssey of Pompe Disease

龐貝氏症的診斷

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Pompe disease is an Autosomal recessive disorder in which mutations in the GAA gene result in deficiency of the enzyme Alpha 1,4 glucosidase. There is a spectrum of severity and the condition can present from infancy to adulthood. The deficiency of Alpha 1,4 glucosidase causes an accumulation of glycogen in cardiac and skeletal muscle. In infants this causes profound hypotonia and hypertrophic cardiomyopathy whilst with age the presentation is largely a myopathy. An early accurate diagnosis is essential particularly in infants since treatment is more effective if started promptly. The differential diagnoses for this condition includes other childhood myopathies.

The management is comprehensive with attention to swallowing, nutrition, respiratory infections, physiotherapy, neurology. Specific treatment with enzyme replacement therapy is associated with improvement in lifespan. In those children at the severe end of the spectrum enzyme therapy is given along with an immune modulation protocol to abrogate antibody response and increase efficacy.

Update on expanded newborn screening and confirmation for aminoacidopathies, organic acidemia and fatty acid oxidation disorders in Vietnam

越南擴大新生兒篩查和確認氨基酸病，有機酸血症和脂肪酸氧化障礙的最新情況

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Vietnam is the easternmost country on the Indochina Peninsula in Southeast Asia. With an estimated 94 million inhabitants as of 2016, it is the world's 13th-most-populous country, and the eighth-most-populous Asian country. Number of birth was about 1.5 million a year. Selected and pilot expanded screening for IEMs has been started in 2004 and 2014, respectively.

Background: The aim of this report is to highlight disease spectrum, confirmation and management experience of several IEMs in Vietnam.

Methods: 4174 high-risk cases (2005-2018) with suspected oganic acidemia (OAs), amino acid disorders (AAs), urea cycle disorders (UCDs) and fatty acid oxidation disorders (FAOD) and 113 229 healthy newborns (9/2014-4/2019) were screened. Dry blood and urine samples were analyzed using MS/MS (amino acid and acylcarnitine analysis) & GC/MS (organic acid anaysis). Mutation analysis was performed for some OAs, AAs, UCDs and FAOD.

Results: OAs, AAs, UCDs and FAOD were identified in 395 cases. 191/395 patients (48.4%) were OAs with 12 different disorders including beta-ketothiolase deficiency (BKT) (58 cases), PPA (33 cases), MMA (22 cases), Isovaleric academia (9 cases), Multiple carboxylase deficiency (MCD) (3 cases). 81/395 patients (20.5%) were amino acid disorders including 64 cases with MSUD, 16 cases with PKU and 1 case with Tyrosinemia type 1. 60/395 patients (15.2%) were UCDs including OTC deficiency (31 cases). 63/395 patients (15.9%) were FAOD. Genotype, phenotype and outcome of management of MSUD and BKT will be discussed.

Conclusion: Treatable conditions of IEMs were most common in Vietnamese patient identified using MS/MS. A specific IEMs laboratory in Vietnam, training for medical staffs, newborn screening, national registry, support group and multidisciplinary care, genetic counseling were scheduled for IEMs patients in Vietnam.

Spectrum of inborn errors of metabolism presenting in the national referral hospital in Malaysia

馬來西亞國家級醫院新陳代謝異常的頻譜

Ngu Lock Hock

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Background: Inborn errors of metabolism (IEMs) are individually rare; however, they are collectively common. More than 1,000 human diseases caused by inborn errors of metabolism are now recognized, and this number is constantly increasing as new concepts and techniques become available for identifying biochemical phenotypes. The aim of this presentation is to determine the type and distribution of IEMs in patients presenting to Hospital Kuala Lumpur, which is the national referral center for diagnosis and management of IEMs.

Methods: Clinical notes of all the patients diagnosed with IEMs for the past 15 years (2003-17) were reviewed.

Results: There were 941 patients diagnosed with IEMs in this 15-years retrospective cohort. Diagnoses were confirmed from biochemical and/or molecular analyses. Of these, 393 patients (42%) were identified to have disorders of intermediary metabolism affecting small molecules; 292 (31%) to have disorders involving primarily energy metabolism; 256 (27%) to have disorders involving complex molecules. The five most common IEMs were maple syrup urine disease, organic acidemias, urea cycle defects, mitochondrial disorders and lysosomal storage disorders. Mucopolysaccharidoses were the most common lysosomal storage disorders.

Discussion: The high prevalence of IEMs in Malaysia requires an urgent need to develop a long-term strategic plan for the prevention of such disorders

Current studies of mucopolysaccharidoses in Taiwan

台灣黏多醣症的研究現況

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In Taiwan, the prevalence of mucopolysaccharidosis (MPS) as a group is reported to be 2.04/100,000 live births, and the most common type is MPS II (52%), whereas in most Caucasian countries, it is MPS I or MPS III. Since MPS is a multisystematic disease, the management of MPS patients requires multiple specialists in the different fields. We aim at the organization of multiple specialists for the most appropriate management, as well as full application of social resources and mental support by social workers.

For subjects who are suspected to be patients with MPS, we collect their urine and blood samples. Accurate confirmative diagnosis relies on detection and quantification of excessive excretion of glycosaminoglycans (GAGs) in urine, urine GAG qualitative analysis to determine the probable MPS subgroups, determination of specific enzyme in leukocytes, serum, or skin fibroblasts, as well as MPS mutant gene analysis. We also developed a rapid, simple, automatic, and reliable liquid chromatography/tandem mass spectrometry (LC-MS/MS) method for MPS phenotype determination according to the predominant disaccharide unit of GAGs, to identify and document the mass spectrum chromatograms for individual MPS phenotypes, and to study the disease severity related to large accumulation of dermatan sulfate, heparan sulfate or keratan sulfate, and their variation after enzyme replacement therapy.

MPS I, II, and VI newborn screening has been executed in Taiwan since August, 2015. The suspicious infants particularly those failed on the recheck of the recalled cases were referred to the confirmative laboratory at Mackay Memorial Hospital for detailed confirmative diagnostic processes, including urine GAGs qualitative/quantitative analyses, leukocyte enzyme activity assay, molecular analysis, echocardiography, X-ray checkups, and physical examinations. We also established a cross-specialty collaboration platform between orthopedic surgeons, rheumatologists, otorhinolaryngologists, cardiologists and medical geneticists based on high-risk criteria for further MPS confirmative diagnosis. Due to the progressive nature of the disease, early diagnosis and early therapeutic intervention, including surgical intervention, rehabilitation programs, symptom-based treatments, hematopoietic stem cell transplantation, and enzyme replacement therapy, are of major importance.

Newborn screening and therapy of SMA in Taiwan

台灣脊髓性肌肉萎縮症新生兒篩檢和治療

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Background: Spinal muscular atrophy (SMA) is the most common fatal autosomal recessive disorder, with an estimated incidence of 1 in 10,000 live births. The disease is caused by absence of a fully functional motor neuron protein gene that produces the survival motor neuron (SMN) protein. SMN protein encoded by two SMN genes: the SMN1 gene, which is the SMA-determining gene, and SMN2 gene. The newborn screening for SMA in one institute of newborn screening center in Taiwan is reported.

Methods: SMA screening started at Taipei Institute of Pathology since August 2017. MassArray method, which checked the SMA allele ratio, were designed for SMA screening, and confirmed by multiplex ligation-dependent probe amplification for the SMN1 and SMN2 copy numbers.

Results: Totally, 82,964 newborns are screened for SMA till March 2019, and the covered rate is 89.3%. For the 7 newborns who were confirmed the homozygous SMN1 gene deletion, 2 have two copies of SMN2, 2 have three copies of SMN2, and 3 have four copies of SMN2. The incidence of SMA is about 1 in 11,852 in Taiwan. Almost all the babies with SMA have 2 copies or 3 copies SMN2 gene had received the SMA therapy. Here, we also demonstrate one SMA type 1, who received the intrathecal therapy successfully.

Conclusion: The implemented newborn screening for SMA showed acceptable and reliable in Taiwan. The importance of early identification from newborn screening leading to early therapy is crucial in clinical practice.

The expanded spectrum of inherited liver disease and improvement in clinical care

遺傳性肝臟疾病之診斷及治療新進展

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In recent 20 years, there have been great advances in the understanding the molecular mechanisms of bile secretion, and an expanded list of inherited cholestatic liver diseases. Progressive familial intrahepatic cholestasis (PFIC) is the prototype of genetic diseases causing chronic cholestasis, liver cirrhosis, and liver failure in childhood or adulthood. Patients manifest jaundice in early childhood, with pruritus, fat and fat-soluble vitamin malabsorption, failure to thrive, and rickets. The first three types of PFICs identified (PFIC1, PFIC2, and PFIC3) represent defects in FIC1 (ATP8B1), BSEP (bile salt export pump, ABCB11), or MDR3 (ABCB4). In the last 5 years, new genetic disorders, such as TJP2, FXR, and MYO5B defects, have been demonstrated to cause a similar PFIC phenotype. Inborn errors of bile acid metabolism cause progressive cholestatic liver injuries mimicking PFIC. Prompt differential diagnosis is important because oral primary bile acid replacement including cholic acid or chenodeoxycholic acid may effectively reverse liver failure and restore liver functions, and avoid liver transplantation. DCDC2 is a newly identified genetic disorder causing neonatal sclerosing cholangitis. The diagnosis of genetic liver diseases has evolved from direct sequencing of a single gene to panel-based next generation sequencing. Whole exome sequencing and whole genome sequencing have been actively investigated. Current treatment modalities include medical treatment, surgery, symptomatic treatment for pruritus, and nutritional therapy. A clinically approved pharmacological chaperone, 4-phenylbutyrate (4-PBA), has been shown to restore the canalicular expression of BSEP. New drug development such as apical sodium-dependent bile acid transporter (ASBT) inhibitor for BSEP defect is underway. Clinical awareness of genetic cholestasis aids in diagnosis, better patient care, development of treatment, and also genetic counseling for patients and families.

Neuronal ceroid lipofuscinosis type 2: History, current status, and future prospects

神經元蠟樣脂褐質儲積症 2 型：過去、現在和未來

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Late infantile-onset neuronal ceroid lipofuscinosis, or CLN2 disease, is a genetic deficiency of the lysosomal enzyme tripeptidyl peptidase (TPP1). Autofluorescent, periodic-acid Schiff positive, sudanophilic storage occurs in cerebral and cerebellar neurons as a result of the deficiency, though the exact substrate and identity of stored substance in CLN2 disease is unclear.

In its classic presentation, typical for patients with complete TPP1 enzymatic deficiency, children initially manifest with speech delay and gait instability prior to age 24 months. With development of epileptic seizures typically between 24 to 30 months of age, rapid and complete neurodegeneration, including retinal vision loss, follow with childhood mortality occurring because of cachexia and aspiration pneumonia. Until recently, treatment was only supportive for CLN2 disease.

CLN2 symptoms, methods of diagnosis, and outcomes of treatment with supportive care and intraventricular recombinant human TPP1 (rhTPP1; Cerliponase alfa) infusions – including safety and efficacy for Cerliponase alfa – will be discussed. Videos representing assessment of CLN2 disease severity and method of central nervous system access for administration of Cerliponase alfa will be presented. The organizational and logistics of a major Cerliponase alfa infusion site will be introduced as well. The outlook for future treatments of CLN2 and other ceroid lipofuscinoses will be examined.

Intelligent genomic medicine

智慧基因體醫學

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Artificial intelligence (AI) has shown great potential in all area of human life, including the biomedical research and clinical care. The technology is particularly required in the analysis of large volumes of medical images, or the deluge of germline and somatic genomics data. AI can be broadly classified as “white box” and “black box” approaches. Methods such as artificial neural networks are often regarded as “black box” solutions where the expressibility of these numerical models still have large rooms of improvement. Yet, the modern artificial neural networks were often designed as an encoder-decoder structure which were particularly useful for extremely complex tasks such as the knowledge representation of the human genome derived from the next generation sequencing data. On the other hand, the “white box” approach offered better expressibility and may be useful for some other medical applications. I have recently developed the generalized iterative modeling (GIM) method, an AI method rooted in the conventional generalized linear models. This method features an iterative shaping of highly-expressive polynominal models with automatically determined combinations of clinical and genomic variables. The models can be written in a few lines of mathematical equations, allowing the interpretation of human experts and the implementations in a wide-diversity of computational platforms. This GIM software is now available for optimizing the U-statistics, F-statistics and the log likelihood in the Cox proportional hazards model, enhancing greatly the traditional analytical approaches such as the generalized linear models..

Innovative renal diagnostic solution for precision management of DKD

創新型診斷方法於糖尿病族群精準腎病管理之應用

Tzu-Ling (Karen) Tseng

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新穎生醫 新竹竹北 台元科技園區 台北南港 國家生技園區

Diabetic kidney disease (DKD) is the leading cause of kidney failure, accounting for more than 40% of new end-stage renal disease (ESRD) incidents. In clinical practice, the persistent presence of albuminuria identified by a random urinary albumin-to-creatinine ratio (UACR) ≥ 30 mg/g is a commonly-adopted diagnostic criterion for DKD. However, UACR alone is not a thoroughly reliable predictor for the progression of DKD. Development of new markers is critical to improve the management of DKD. Bio Preventive Medicine Corp.(BPM) is a spin-off derived from a national biomarker research program focus on CKD. BPM has been translating validated and IP-protected biomarkers into diagnostic solution for unmet clinical needs, including DKD. In this talk, I will overview the development of novel renal biomarkers at BPM. The role of the novel BPM renal biomarker, DNlite IVD103, on risk assessment of DKD and renal function progression in patients with T2DM will be discussed in this presentation.

Flagship program of precision medicine in Taiwan

精準醫療旗艦計畫

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We are all at risk for certain diseases, be it cancer, heart attack, stroke, or infection. The risk of being affected with certain diseases depends on the environmental exposure, behavior, and predictably, one's genetic make-up. With the current technology, it is possible to determine the 3 billions bases of each individual's genome, at an affordable price to determine the risks for the above-mentioned diseases. The genomic data provide much useful information, and the new technology has a significant impact on health care management, at both individual level and at the population level.

With the successful implementation of the Flagship Program on Precision Medicine, we have networked with Taiwan Foundation for Rare Disease and Taiwan Human Genetics Society to from Taiwan Rare disease network (TRDN). Over the past two years, we offered WGS to more than 100 families affected with rare or undiagnosed diseases, and our pilot study has provided genetic diagnosis for nearly 60% of the cases, who otherwise had no idea about what kind of disease they have had and what went wrong in their genes.

To illustrate the principle of how whole genome sequencing (WGS) can help a patient with familial (genetic) disease, here we provide two stories of epilepsy and dementia. There are many patients affected with these not-so-common conditions, which give the patients and the family members a big burden. Epilepsy affects over 200,000 individuals and dementia many more. However, not all the patients have a family history or a "mutation" in their genomes. A small fraction of them do show a family history and have a disease onset at relatively young age, and they are likely to be benefited by having a "definitive" diagnosis for better treatment and management of the "difficulty" – including choice of marriage and decision to have a baby, job, and insurance.

What are the values for providing a "definitive" diagnosis to a family? From our working experiences, we found that it is possible to have the following: 1. optimizing medication; 2. improving clinical management 3. offering prenatal diagnosis; 4. conselling at reproductive clinics; 5. understanding disease pathogenesis ; 6. facilitating drug development.

Our project has put Taiwan on the map. We are a leading country in Asia to apply genomics technology and precision medicine to the "patients", and potentially, to establish a system to provide a cost-effective service to the families who are in need of medical care and social support. There are many challenges ahead, but our vision and execution of the government policy should align well with the global trend, for example, the UK NHS system. With further improvement and additional investment, we could move forward toward not only better health care management but also an opportunity to developing biotechnology through precision medicine and big data analysis.

6

新式放射線治療研討會：
國際醫療交流暨粒子性放射治療

Symposium for New Radiotherapy Era: International Medical Exchange and Particle Radiotherapy

主辦單位：臺北榮民總醫院 腫瘤醫學部

時 間：108年6月22日 08:15~12:00
Time：June 22, 2019 08:15~12:00

地 點：台北國際會議中心 103 會議室
Place：Conference Room 103
Taipei International Convention Center

新式放射線治療研討會：國際醫療交流暨粒子性放射治療

Symposium for New Radiotherapy Era: International Medical Exchange and Particle Radiotherapy

Stereotactic ablative radiotherapy (SABR): Evolution in oncology treatment

立體定位放射治療：越南經驗

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越南胡志明市大水鑊癌症中心

Background: In the treatment of cancer, advances in radiotherapy techniques, chemoradiation, image guided radiation therapy, and control of tumor movement have increased the time of disease control as well as the overall survival time. Recently, with stereotactic ablative radiotherapy (SABR), the opportunity for treatment of cancer with medically inoperable early stage or oligometastases has been increased clearly. The mechanism of SABR alone or combination with chemotherapy or immunotherapy has become the key points of many studies. The clinical trials to demonstrate the efficacy of SABR versus standard treatment have been ignored, therefore, the important questions remain unanswered. This article reviews the role of SABR and Estimating of SABR outcomes as treatment for cancer patients at Cho Ray Cancer Center.

Methods: Prospective Case Series of 8 SABR patients at Cho Ray Cancer Center from 01.01.2018 to 31.12.2018.

Results: Of the 8 SABR patients, these were 3 lung cancer patients, 1 lung metastases, 2 brains metastases and 2 liver metastases. The Responses of 3 lung cancer patients : Complete Response (CR); 1 lung metastases patients : Partial Response (PR); 2 brains metastases : 1 CR and 1 PR ; 2 liver metastases:1 CR and 1 PR. One patient has “Abscopal Effect”. All patients have survived and worked normally after 1 year of follow-up.

Conclusion: SABR is a safe, effective and highly responsive treatment method. This is a revolution in cancer treatment in the future.

Clinical trials for treating recurrent head and neck cancer with boron neutron capture therapy using the Tsing-Hua Open Pool Reactor

硼中子捕獲治療：頭頸癌經驗

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Head and neck (HN) cancer is an endemic disease in Taiwan. Locally recurrent HN cancer after full-dose irradiation poses a therapeutic challenge, and boron neutron capture therapy (BNCT) may be a solution that could provide durable local control with tolerable toxicity. The Tsing-Hua Open Pool Reactor (THOR) at National Tsing-Hua University in Hsin-Chu, provides a high-quality epithermal neutron source for basic and clinical BNCT research. Our first clinical trial, entitled "A phase I/II trial of boron neutron capture therapy for recurrent head and neck cancer at THOR", was carried out between 2010 and 2013. A total of 17 patients with 23 recurrent HN tumors who had received high-dose photon irradiation were enrolled in the study. The fructose complex of l-boronophenylalanine was used as a boron carrier, and a two-fraction BNCT treatment regimen at 28-day intervals was used for each patient. Toxicity was acceptable, and although the response rate was high (12/17), re-recurrence within or near the radiation site was common. To obtain better local control, another clinical trial entitled "A phase I/II trial of boron neutron capture therapy combined with image-guided intensity-modulated radiotherapy (IG-IMRT) for locally recurrent HN cancer" was initiated in 2014. The first administration of BNCT was performed according to our previous protocol, and IG-IMRT was initiated 28 days after BNCT. As of May 2017, seven patients have been treated with this combination. The treatment-related toxicity was similar to that previously observed with two BNCT applications. Three patients had a complete response, but locoregional recurrence was the major cause of failure despite initially good responses. Future clinical trials combining BNCT with other local or systemic treatments will be carried out for recurrent HN cancer patients at THOR.

BNCT is a treatment option for recurrent malignant brain tumors

硼中子捕獲治療是復發惡性腦瘤的治療選擇

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Radiation therapy plays an important role in standard cancer treatment. However, patients who are resistant to traditional radiation therapy or who have relapsed after conventional radiation therapy are often encountered in clinical practice. There is therefore a need for a new radiation therapy for this type of patient. Although boron neutron capture therapy is not a new concept of radiation therapy, due to technological breakthroughs and conceptual improvements at the start of the 21st century, this therapy, which covers multidisciplinary technologies, such as medical physics, atomic science and technology, boron-containing drug synthesis, radiobiology, and clinical oncology has advanced greatly, and has gradually matured to a clinically useful therapy for patients with cancer.

Since March 2017, Taipei Veterans General Hospital and Nuclear Science & Technology Development Center in National Tsing Hua University have been collaborating to conduct an emergent BNCT model for recurrent malignant glioma patients (for both children and adults). This treatment model is approved by the IRB (Institution Review Board) of Taipei Veterans General Hospital and TFDA (Taiwan's Food and Drug Administration) after special application. Up to now, we already treated for 20 brain patients (including three pediatric patients) with this compassionate use.

Here we'd like to share our clinical experience and hope to promote this unique targeted particle radiotherapy in the future for our CNS tumor patients.

Heavy ion therapy center in Osaka

大阪重粒子中心介紹

Junetsu Mizoe

溝江純悦

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The heavy ion radiotherapy using carbon ions has been started at Osaka Heavy Ion Therapy Center since October 16th, 2018. The main accelerator is a synchrotron (by HITACHI) with a diameter of 17 meters and a circumference of about 57 meters. The synchrotron was installed in a compact and narrow space and can accelerate carbon particles up to about 70% of the light speed. There are three treatment rooms, consisting of two rooms with horizontal and vertical ports, and one room with horizontal and 45-degree ports.

Carbon ion radiotherapy has fewer side effects than conventional radiotherapy, and good treatment results can be obtained for the cancer that could not be provided sufficient effects with conventional surgery and radiotherapy.

Till the end of March 2019, a total of 147 patients were enrolled into the carbon ion radiotherapy. They consisted of 110 patients of the prostate, 12 of the Head & Neck, 8 of the lung, 5 of the pancreas and others like the liver, the Bone & Soft Tissue tumor and the kidney.

The average number of fractions is about 12 fractions through 3 weeks with four times a week. For the early peripheral non-small cell lung cancer can be treated by single fraction in one day and the peripheral hepatocellular carcinoma will be treated by 2 fractions in 2 days. All ports are raster scan method and can be treated with good dose distribution. Furthermore, we are aiming for hypo-fractionated irradiation as few as possible using maker tracking system for the lung, the liver and the pancreas. We will provide advanced cancer treatment from Osaka to all over the Japan and to the world with a gentle and effective treatment by carbon ion radiotherapy for many patients.

Current status of 1st carbon ion therapy in Korea: Yonsei cancer center

韓國第一台重粒子設備近況：延世癌症中心

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琴雄燮

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Charged particles can achieve better dose distribution and higher biological effectiveness compared to photon and proton radiotherapy. Carbon ions are considered an optimal candidate for cancer treatment using particles and currently eleven carbon ion centers (5 in Japan, 4 in Europe and 2 in China) are in operation at this moment.

Yonsei Cancer Center, which has persistently invested to present the state-of-the-art instruments and new technique to Korea, decided to introduce the 1st Carbon ion therapy to Korea in 2016 and completed the final contract in March, 2018 after 2 years' discussion and investigation.

The awarded heavy-ion therapy system will be equipped with one horizontally-fixed beam treatment room and two superconducting rotating gantry treatment rooms. The most highly-advanced technologies such as quick-and-accurate patient positioning, 3D high-speed scanning irradiation, respiratory gating and rotating gantry, have been already utilized in the facilities and will be applied to Yonsei Cancer Center. Especially, the downsized rotating gantry owing to superconducting magnets and an advanced irradiation nozzle are the key differentiators of Yonsei Cancer Center for patient's comfort and high throughput. The heavy-ion therapy facility with two rotating gantry treatment rooms will be the first in the world and the first treatment will start in 2022.

Heavy-ion therapy, known as the most advanced cancer treatment in the world, will deliver the promise of patient-centered care in an era of incurable cancer and super-aging society in Korea and we are hoping to bring breakthrough innovations in cancer.

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「2019年3C科技產業於醫學教育訓練之創新與應用」跨領域國際醫學教育研討會

The Innovation and Applications of 3C Products in Medical Education

時 間：108年6月22日 08:20~17:40

Time：June 22, 2019 08:20~17:40

地 點：台北國際會議中心 105 會議室

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Taipei International Convention Center

「2019年3C科技產業於醫學教育訓練之創新與應用」跨領域國際醫學教育研討會

The Innovation and Applications of 3C Products in Medical Education

What's the impact of information system construction on the Big Data Center of the Taipei Veterans General Hospital?

臺北榮總大數據中心資訊系統

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Clinical Big data collection relies on the results of clinical trials and observational studies of administrative databases. However, these studies not only require many valuable resources but are usually time-consuming and cumbersome.

We try to build the infrastructure of the computer system called Big Data Center System (BDCS) at the Taipei Veterans General Hospital (VGH-TPE) in Taiwan. Multiple electronic healthcare databases are built into a Common Data Model (CDM) by applying the databases schema and coding book used in the Taiwan National health insurance research database (NHIRD) that maintains the anonymity and the confidentiality of each data containing sensitive information in a medical database.

BDCS was developed using a CDM, which transforms data from different sources into an NHIRD standardized format and facilities the implementation of standardized computer programs by automatically removing, generalizing, and expanding information. It is designed to enhance data privacy protection to a data warehouse and handle queries automatically.

We developed the infrastructure of the BDCS, including an integrated data warehouse and a surveillance workflow. BDCS supports a diverse range of analytic studies spanning from epidemiology, clinical decision-rule improvement, to electronic tool development. It is notable for three factors: (1) Simply removing all explicit identifiers before the release of the data is not enough to preserve the data confidentiality. (2) Including a diverse and large patients population. (3) Containing time series data including laboratory results.

The BDCS systems can integrate the workflow of cohort identification and CDM to accelerate the survey process of time-consuming and security engineering. Common data model and BDCS platform of VGH-TPE are built to advance the use and performance of healthcare data in improving patient care of artificial intelligence in medicine.

Deep learning in medical imaging: An overview of concepts and educational experiences from Taiwan AI academy

深度學習於醫療影像中的應用：觀念概述與台灣人工智慧學校教學經驗分享

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Machine learning (ML) is a rapidly growing field of computer science recently due to the availability of large-scaled datasets and advances in the computation hardware. Its applications have become ubiquitous in our daily life from automated machine translation, vision and speech recognition, matching news items, to email spam-filter and so on. By feeding in a large amount of data (or features), ML algorithms can learn to condense them into a more accessible or meaningful form, such as distinguishable class labels or patterns. In particular, a neural network-based learning method, called deep learning (DL), are composed of several simple but non-linear modules and are able to effectively learn suitable representations from complex raw data and distill essential information. DL approach has shown its superior ability to accomplish those tasks related to images and often exceeds human performance.

Currently, the medical system is also experiencing the so-called Information Age, with the exponential increase in textual and visual digital information. It becomes quite impractical to humanely categorize such exploding amount of data. In particular, since the medical image analysis relies heavily on extracting useful information from images, it is a rather natural field in which DL could assist. In this talk, we introduce key concepts of DL with emphasis on the convolutional neural networks and show how the learning algorithm can automate tasks that biological visual systems can do. We demonstrate the advantages brought by DL approach through a few concrete examples such as the fields of radiology and ultrasound. Furthermore, we briefly discuss opportunities and challenges one might confront with when seeking to incorporate DL technique in the medical imaging practically. Finally, we share our educational experiences for nurturing AI talents in Taiwan and hope to provide some insights for medical education in the near future.

From teaching to innovation: VR development and application in Taipei Medical University

由教學到開發：VR 研發與應用在臺北醫學大學

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The last 5 years have been witness to the unprecedented growth of Virtual Reality (VR) in many fields including entertainment, military, healthcare, design and education among many others. But this is not a new trend, virtual reality and it's related technologies, Augmented Reality (AR) and Mixed Reality (MR), have been in development since the 1960s, but adoption had been slow due to technological constraints and high costs.

Today, the necessary technology for large scale implementation of VR is readily available at accessible prices, making it an ideal time for healthcare educational institutions to begin investing in this technology that could potentially revolutionize the way health professionals are trained and assessed.

There are several advantages to the use of VR and it's related technologies for training health professionals which can provide cost-effective solutions to address the current and future needs in health professions education such as adaptive learning, immersive educational environments, early clinical exposure and comprehensive competency-based assessment. Yet there are also many challenges to be overcome, such as a lack of clear educational frameworks for VR, limited evidence of effectiveness, high development costs of VR applications and lack of trained faculty.

At the Center for Education in Medical Simulation (CEMS) at Taipei Medical University, we have developed a cutting-edge VR initiative focusing on overcoming the challenges of the adoption of this technology and developing the next generation of applications and theoretical frameworks to allow it's implementation following an evidence-based approach and in-line with best practices in clinical skills training, paving the way for future mainstream adoption of these promising technologies and the important benefits they may bring to the training and assessment of the healthcare workforce of the future.

Digital skills and competence for future medical practitioners

醫學數位資訊技能的養成與教育

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Digitization is affecting almost every aspect of people's live, work and influencing our decisions-makings, medicine is also changing along this digital path. New biomedical technologies are developing faster than ever before, which will, no doubt, substantially affect future healthcare professionals of medical doctors. To enable future doctors to comply with such paradigm shift from traditional to digital healthcare, an innovative curriculum was designed and developed and first implemented at the MacKay Medical College in 2018-batch medical students and also at MacKay Medical Hospital from 2017. The education concept encompasses three modules - UGY curriculum for digital health, medical teachers as a designer training, and a workforce for digital health innovations and implementations. The teaching of digital skills is a relevant new component of curriculum reform in medical educations. The competency development requires a systematic educational structure, including need exploration, technical support, and application delivery.

Virtual Neuro-navigation in reality surgery

虛擬實戰 與神同行

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The 3D virtual image system is prevailing at current modern surgeries. With improvements in computational power and advances in visual and haptic display technologies, virtual surgical environments can now offer potential benefits for surgical training, planning, and rehearsal in a safe, simulated setting. It is readily compensated by provide depth perception and stereotactic visualization to the operator. **Neural tract is invisible under the microscope except visualized by virtual tractography by computing methodology**. Diffuse tensor images (DTI) are the source to make the tensor neural tract being able to see after combination of current navigation system – we named : **Virtual Neuro-navigation**. Even though the innovative development, the surgeon still needs to overcome the learning cascade.

Between 2015 and 2017, 120 patients were selected and underwent VR Neuro-navigation Surgery (VRNAS). We performed VRNAS by aids of virtual 3D conversion simulator (SHINKO, Tokyo, Japan) with head-mounted display (HMD, SONY-HMZ, Tokyo, Japan) visualization. The peri-operative maneuverability (score 0-4) was compared to the other standard surgeries purely by standard navigation system with no VR assistance. The operator's discomfort (cybersickness) in this adaptation to the new approach was also analyzed. The flow of procedure and complications were recorded at outpatient follow-up.

All patients experienced neurologic improvement after the operations. 79 patients had no recurrence and hormonal balance at serial follow-ups, 23 patients underwent postoperative stereotactic radiosurgery on account of residual tumor. There was no catastrophic vascular conflict and major complications (CSF leaks, bacterial meningitis, stroke…etc) in our cohort. The mean operation time and maneuverability were comparable with our controlled group (p=0.01). With regard to the wearing limitation, repeated training can vanish the cybersickness and it is associated with the individual tolerance.

The use of the VRNAS integrated the VR and real-time navigation technology showed the comparative benefit in accuracy and patients' outcome. We believed there is great promising potential to mature this novel technology to guarantee the patient's safety.

Application of Google forms and automated Google App script in a workflow for clinical core competency milestones assessments

應用 Google 表單與自動化 Google App 程式語言執行臨床核心能力里程碑評估

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Competency-based medical education (CBME) has emerged as a mainstream method for educating and assessing the next generation of physicians. We developed the first Integrated Traditional Chinese version of Otolaryngology Milestone (ITCOM) project in Taiwan in June 2017, addressing 21 subcompetencies and 368 milestones. The results of the three biannual assessments between July 2017 and September 2018 revealed that all otolaryngologic resident physicians exhibited significant improvements in milestone achievement. However, frequent grading errors were found during the self-evaluations and reevaluations. Moreover, the waste of paper was against the trend for environmental protection.

About six months ago, we initiated an interdisciplinary project, aiming at a paper-free, simplified workflow of milestone assessments with increased accuracy of scoring. Several online questionnaire services were compared, namely Google Form, SurveyCake, Typeform, ZOHO, SurveyMonkey, Wufoo, Formsite, FormExperts, JotForm, and Airtable. Considering the flexibility, expandability and user experience, we decided to use Google Form accompanied with other services in Google G suite as the framework of the system. Google Spreadsheets not only allows us to access and edit spreadsheet files anytime, anywhere, but also with the customization program written in Google App Script, which can define the scoring algorithm and automatize the workflow of self-evaluations and reevaluations. With the help of the Social Networking App: Line, the resident physicians and the faculty members can access the forms anytime, anywhere, and focus only on the description of each milestone, without the need for the decision of grading. The results of the automatic scoring via cloud computing will be stored in Google Drive.

The future application of our workflow will be a universal comparison of the attainment of core competencies, with milestones or entrustable professional activities, among different institutions without the limitation of the individual healthcare information system. Most importantly, all these online services were free of charge.

The application of virtual reality in microteaching of faculty development

虛擬實境在教師微觀教學上的運用

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Virtual Reality has been broadly applied in entertainment, but the experience of applying in medical education, especially in faculty development, is few. Taipei Veterans General Hospital built an innovative classroom and new training module for faculty development in 2011. We would like to share our experience in application of virtual reality classroom in microteaching of faculty development. The virtual reality classroom is a space with integration of high technology. We used six projectors and six short video clips to create five simulated situations of clinical teaching, including bedside teaching, outpatient clinic teaching, lecture-based teaching, operatory room teaching, emergency room teaching. For the virtual reality classroom, we also create many teaching case scenarios simulating the real teaching situation.

To apply the virtual reality classroom in microteaching, we invited simulated patients and simulated students to role-play in each case scenario. In each training, a senior faculty is the facilitator in the small group discussion, in charge of facilitating the teaching, assessing process and giving feedback to the attendants of the instructional skills course or workshop and guiding the small group discussion. The whole process is directly observed by other peers through one-way mirror and video-recorded. The teaching process can be dissected into several sections and reviewed by the teacher, the peers and the facilitators. With the virtual reality classroom, we built a successful model for training faculty of different medical professionals.

In conclusion, virtual reality can not only be applied in entertainment but also be used in the clinical faculty training. New technology makes faculty training easier and more effective. This is an innovative and creative training module in Asia. Guests from different countries were amazed by the design. We would like to share our experience of applying this training model and hope you enjoy it.

Pedagogy and experiences of creation of XR materials for education and holistic care in Intelligent hospital

智慧醫院裡研發 XR 虛擬實境教材的教育學理論及北榮推廣經驗分享

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Extended reality (XR) is the combination of digital and bio-reality experience through technology. Today's advances in technology can create augmented reality (AR) and virtual reality (VR), mixed reality (MR) soft and hard ware. With the XR tools, the users can bring digital objects to the physical world or bring physiological world objects to the digital world. XR Technology has applied these tools to education, training and medical care.

In addition to optimizing teaching content (beyond lecture, video, book, etc.), XR attracts trainees' attention and engagement, expect to reach goals of Miller's pyramid including Knows, Knows how, shows how, does. XR, as a simulation tool can achieve steps of Bloom's Taxonomy theory including **r**emember, **u**nderstand, **a**pply, **a**nalyze, **e**valuate and **c**reate. Finally, OSCE is used to achieve the evaluation of Kirk Patrick's model. Overall, XR-based technology-enhanced education emphasized steps of discovery, integration, application (transfer), teaching and digital (practice) in the smart hospital. The essence of medical education includes educating health caregivers and patients. In addition to video gaming, the use of XR in healthcare/education has increased significantly in recent years. Taipei Veteran General hospital (TVHG) innovated XR simulation Education area has a surreal design space. The XR and various vehicles can be integrated through information and cross-platform to inspire the creation of XR in this area. In addition to planning a series of lectures across the information technology community, the TVGH has created the first wave of bilingual XR material for education of trainees, health professionals, patients or families. The content including details of difference between tracheotomy and general intubation; home care for tracheotomy; soft bronchoscopy; oral cancer, early kidney cancer, atrial fibrillation, how to avoid needle sticks, and the correct classification of medical waste.

Patients, data, and machines: New models for 21st century medical education

智慧醫療下人文教育相關主題

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New technologies have created major shifts in societies around the world, giving patients new voices and creating opportunities for data-driven decision-making. These developments are forming new relationships between humans (clinicians and patients) and technologies (artificial intelligence/machine learning, care robots, and wearable connected devices). The practice of medicine, like many fields, has undergone a shift in the past couple of decades, moving toward a less hierarchical and more distributed approach to knowledge and expertise. Partly enabled by technologies including the internet, fiberoptics, and robotics, this shift has fundamentally changed the clinical experience in hospitals throughout the developed world. Medicine has become technologically mediated.

This shift had implications for doctors, nurses and for patients. For health professionals, clinical environments became populated with screens and devices, whose concepts and technical specificities came from outside of medicine. For patients, care became less about a human encounter and more about a technological encounter.

Many have described these shifts as the preconditions that have led to the entry of "human centered design" (HCD) into healthcare, because while this term has many meanings, one is that it is a collaborative creation of technologies or processes that puts the end user at the center of the action. HCD helps technology companies avoid producing devices that don't meet their end users' needs. HCD also helps healthcare professionals avoid being forced to adopt new technologies that are minimally helpful to them or their patients. These changes seem logical, as they would save time and money (and frustration). But how to implement these changes depends on the answer to the question, who is the end user in healthcare? In the case of clinical ecosystems, of course we would say that the patient is the end user. Without patients, what would be the purpose of healthcare?

But in the context of a high-tech neurosurgical suite, the end user might be more appropriately understood as the surgeon, the anesthesiologist, the circulating nurse, or other medical professionals who are using technologies to provide patient care. However, clinicians and designers who do "human centered design" work in medicine often argue that this idea of a divide between clinical perspectives and needs and patient perspectives and needs is unfounded and in fact counterproductive. Moreover, when one starts to experiment with the techniques of human centered design in medicine, one sees that the same approach works when trying to solve a problem that patients experience and when trying to solve a problem that clinicians experience. And when members of those different groups collaborate on design together, the results tend to be better than when either group works alone.

How might medical educators integrate emerging methods such as human-centered design into training practices for future healthcare providers? What new forms of knowledge do 21st century learners need to develop, and how might they best develop them? This talk will describe the emerging domains of expertise that must be integrated into health professions education, along with some new approaches to cultivating digital health literacies. In particular, the lecture will explain how emerging medical technologies have been integrated into healthcare in the past, as a way of understanding how new technologies like care robots, wearables, and AI can be integrated into healthcare in the future using human-centered design.

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腎臟精準醫學

Precision Medicine in Nephrology: Latest Research in Kidney Gene Regulation and Vascular Access Malfunction

時 間：108年6月22日 08:40~12:00
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Taipei International Convention Center

腎臟精準醫學
Precision Medicine in Nephrology: Latest Research in Kidney Gene Regulation and Vascular Access Malfunction

Single-cell transcriptomics of the kidney reveals unexpected cellular targets of kidney diseases

單細胞基因轉錄組分析在腎臟學的應用

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Our understanding of kidney disease pathogenesis is limited by an incomplete molecular characterization of the cell types responsible for the organ's multiple homeostatic functions. To help fill this knowledge gap, we characterized 57,979 cells from healthy mouse kidneys by using unbiased single-cell RNA sequencing. On the basis of gene expression patterns, we infer that inherited kidney diseases that arise from distinct genetic mutations but share the same phenotypic manifestation originate from the same differentiated cell type. We also found that the collecting duct in kidneys of adult mice generates a spectrum of cell types through a newly identified transitional cell. Computational cell trajectory analysis and in vivo lineage tracing revealed that intercalated cells and principal cells undergo transitions mediated by the Notch signaling pathway. In mouse and human kidney disease, these transitions were shifted toward a principal cell fate and were associated with metabolic acidosis.

Epigenetics in kidney development and renal disease

表觀基因學在腎臟學門的進展

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Several types of epigenetic marks facilitate the complex patterning required for normal human development. These epigenetic marks include DNA methylation at CpG dinucleotides, covalent modifications of histone proteins, and noncoding RNAs (ncRNAs). They function in a highly orchestrated manner, regulating mitotically heritable differences in gene expression potential without altering the primary DNA sequence. To identify functionally important epigenome-modifying enzymes and genome regions where methylation modifications are functionally important for kidney development, we performed genome-wide methylation analysis, expression profiling, and systematic genetic targeting of DNA methyltransferases (*Dnmt1*, *Dnmt3a*, and *Dnmt3b*) and Ten-eleven translocation methylcytosine hydroxylases (*Tet2*) in nephron progenitor cells (*Six2* ^{Cre}) in mice. We found dynamic methylome changes on promoters and enhancers during development. *Six2* ^{Cre}*Dnmt3a* $^{f/f}$, *Six2* ^{Cre} *Dnmt3b* $^{f/f}$, and *Six2* ^{Cre} *Tet2* $^{f/f}$ mice showed no significant structural or functional renal abnormalities. In contrast, *Six2*^{Cre} *Dnmt1* $^{f/f}$ mice died within 24 hours of birth, from a severe kidney developmental defect. Genome-wide methylation analysis indicated a marked loss of methylation of transposable elements. RNA sequencing detected endogenous retroviral transcripts. Expression of intracellular viral sensing pathways (RIG-I), early embryonic, nonrenal lineage genes and increased cell death contributed to the phenotype development. In podocytes, loss of *Dnmt1*, *Dnmt3a*, *Dnmt3b*, or *Tet2* did not lead to functional or structural differences at baseline or after toxic injury.

Update of AV fistula creation and maintenance

自體動靜脈內瘺管建立與維護

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劉同強

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The arteriovenous fistula(AVF) is currently the best permanent access for the hemodialysis patient. With the increasing proportion of elderly and frail patients on hemodialysis, the rate of failure to mature has increased with a decrease in patency rates. Moreover, fistula complications are associated with morbidity, mortality, and a high economic burden. The ability to preoperative manage, routinely monitor and salvage failing AVFs is important to achieving successful AVF outcomes. This lecture includes the following:

1. AVF first
2. Preoperative assessment for AVF
3. Creation of AVF
4. Physical examination of AVF
5. Ultrasound surveillance protocol for evaluating AVF
6. Diagnosis and management of AVF complications

Engineering precision medicine for HVA complications

精準醫學工程技術應用於血液透析血管通路併發症

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Hemodialysis is an efficient treatment for kidney failure; the access is a surgically created vein used to remove and return blood during hemodialysis. There are two types of vascular access designed for long-term use, namely the AVF and the AVG. However, the AV shunt, either by AVF or AVG, would also result in disturbed flow at the AV junction region which causes endothelial cell (EC) dysfunction and smooth muscle cell (SMC) hyperplasia resulting in hemodialysis vascular access dysfunction which is a major cause of morbidity and mortality in hemodialysis patients. Thus, our study aims investigate the hemodynamic properties (i.e., disturbed flow and wall shear stress) in/near AV shunt by using computational fluid dynamics (CFD) simulations based on computerized tomographic angiography (CTA) images, design and optimize the structure of 3D-printed AV shunt for reducing disturbed flow resulting in pathophysiological events lead to neointimal hyperplasia and thrombosis, and ultimately vascular stenosis. Instead of ePTFE graft, the designated 3D-printed arteriovenous graft using biocompatible polymers based on the CFD simulations had been implanted into pig successfully, which is the first animal model study in Taiwan.

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腫瘤診治的最新進展

Recent Advances in Diagnosis and Treatment of Tumors

時 間：108年6月22日 08:30~12:10

Time：June 22, 2019 08:30~12:10

地 點：台北國際會議中心 201B 會議室

Place：Conference Room 201B
Taipei International Convention Center

腫瘤診治的最新進展

Recent Advances in Diagnosis and Treatment of Tumors

Updates on the role of cancer-associated fibroblasts in cancer biology and immunotherapy

腫瘤相關纖維母細胞在腫瘤生物學與免疫治療的角色與最新進展

Jiun-I Lai

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Cancer therapeutics have improved significantly in the past decade, especially due to the success of immunotherapy. The advent of immunotherapy have opened a new avenue of therapeutic opportunity in targeting the tumor microenvironment. The tumor microenvironment includes blood vessels, immune cells, fibroblasts and the extracellular matrix (ECM) that surround cancer tissue. Cancer associated fibroblasts (CAFs), previously thought as innocent bystanders, have now been proposed to play a role in modulation of tumor microenvironment, confering resistance to chemotherapy and immunotherapy, and participates in angiogenesis and metastasis. In general, CAFs possess a general immunosuppressive and tumor promoting feature, and actively engages with other constituents in the microenvironment (including macrophages) to promote tumor progression and metastasis. In this regard, therapeutics targeting CAFs could have the potential to enhance the efficacy of immunotherapy. Multiple clinical studies are currently undergoing to probe the potential of targeting CAFs in cancer treatment.

Besides the role in immunomodulation, CAFs also confer resistance to cytotoxic chemotherapy agents and thus negatively impacts patient outcome. Emerging studies provide encouraging evidence that targeting CAFs could also play a role in improving responses towards cytotoxic chemotherapy, and active therapeutics development in this area is ongoing.

In this presentation, I will present the recent advances regarding the role of CAF in cancer biology with a focus on therapeutic development and clinical studies. Recent experimental data suggest that CAFs are highly heterogeneous and might differentially impact results of therapies targeting CAFs. With further advances in this field, therapies that differentially targets distinct CAF subtypes could potentially lead to a personalized and efficacious treatment for human cancers.

Systemic treatment of advanced non small cell lung cancer in Viet Nam

在越南非小細胞肺癌的全身性治療

Pham Tuan Anh

Department of Medical Oncology,
Vietnam's National Cancer Hospital (K Hospital), Vietnam

Lung cancer is the most common cancer and the leading cause of cancer death among both men and women in the world. According to the International Agency for Cancer Research (IARC), there are about 24,000 new cases and 21,000 deaths per year from lung cancer in Vietnam. Although metastatic lung cancer has not been curable yet, in the last 10 years, we have seen many amazing achievements in the systematic treatment of lung cancer to prolong survival and improve the quality of life for patients. Those are targeted TKI therapy and immunotherapy (checkpoint inhibitor). In Viet Nam, these drugs are available but challenge is developing evidence-based guidelines adapted for circumstances in Viet Nam, a lower middle-income country. We try to refine and merge the international guidelines and our own practices appropriate for Vietnamese patients within available resources.

Negative lymph nodes count and lymph node ratio are associated with the survival in male breast cancer

淋巴結數目為零及數目比例與男性乳癌存活率之關連性

Sang Kim To

Ho Chi Minh City Oncology Hospital, Ho Chi Minh City, Vietnam

Background: Male breast cancer (MBC) is usually diagnosed in late stages and therefore it has a worse prognosis than female breast cancer (FBC). It is more likely to have lymph node (LN) involvement compared to FBC.

Methods: We aimed to disclose the prognostic role of examined LNs (ELNs), negative LNs (NLNs) and positive LNs (PLNs) counts, and LNs ratio (LNR), defined as (PLNs/ENLs), on the survival rate among MBC patients through this large population-based study using the data from Surveillance, Epidemiology, and End Results program.

Results: Older age, black patients with stage IV, ≤1 NLN, and >31.3% LNR were significantly associated with a worse survival across all prediction models. Moreover, we demonstrated a decreased risk of mortality in MBC patients across the MBC-SS (HR, 95% CI=0.98, (0.96, 0.998), P=0.03) and the 10-year MBC-SS (HR, 95% CI=0.98, (0.96, 0.999), P=0.04) models.

Conclusion: MBC has an augmented incidence over years. We have disclosed several independent predictors of MBC survival including age, race, stage, NLNs, and LNR. We strongly suggest adding the NLNs count and/or LNR into the current staging system. Further studies need to shed the light on mechanisms underlying the association between the NLNs count, LNR and MBC survival.

FOLFIRI chemotherapy in patients with advanced gastric cancer: Vietnamese experience

進展性胃癌病人 FOLFIRI 化學治療：越南經驗

Nguyen Van Hung

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Background: (1) To evaluate treatment results and factors related to survival of patients with advanced gastric cancer treated FOLFIRI regimen. (2) To report toxicity of FOLFIRI regimen in treatment of patients with advanced gastric cancer.

Methods: Clinical description study of 44 advanced gastric cancer patients treated with FOLFIRI regimen.

Results: Overall response rate was 36.4%, in which 4.6% patients had complete response. Stable disease rate was 15.9%, and 47.7% patients had progression. Progression-free survival median was 5.1 months. Pathological type and sex were related to progression-free survival. The proportion of grade 3, 4 neutropenia were 6.1% and 4.9%. Rate of grade 3, 4 AST and ALT elevation were below 1%. Grade 4 diarrhea was 0.4%. There was no case of other adverse effects with grade 3, 4.

Conclusion: FOLFIRI regimen had good responses and improved patient's progression-free survival, together with acceptable toxicity in patients with advanced gastric.

What's new in hepatocellular carcinoma? Target therapy and immunotherapy

肝癌的嶄新治療：標靶藥物與免疫治療

San-Chi Chen

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Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. The only curative treatment modalities for HCC are surgery, percutaneous ablation, and liver transplantation. Unfortunately, the majority of patients have unresectable disease at diagnosis. Therefore, effective treatment options are needed for patients with advanced HCC. In the past decade, the only one standard treatment for patients with advanced HCC is the multikinase inhibitor (MKI), sorafenib. Due to the limited treatment response and toxicities, other alternative therapies are required.

Recently, many drugs of multi-kinase inhibitor (MKI), immune checkpoint inhibitor (ICI) and monoclonal antibody have shown favorable results in advanced HCC patients. In this presentation, I will share the newest clinical trial data of multi-kinase inhibitors (regorafenib, lenvatinib, cabozatinib), monoclonal antibody (ramucirumab), immune checkpoint inhibitors (nivolumab, pembrolizumab). Combination therapy including MKI plus ICI, monoclonal antibody plus ICI and ICI plus ICI will be discussed as well. I will also share the Taipei Veterans General Hospital experience using the above novel modalities.

A survey of clinical research on CAR-T cell therapy in Chinese Mainland

CAR-T 細胞療法在中國大陸的臨床研究概況

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In recent years, immunotherapy as a new cancer treatment has attracted extensive attention from researchers. In all kinds of the immunotherapy that act on tumors micro-environment, chimeric antigen receptor-modified T cells (CAR-T) are favored, and are being tried in various cancers therapy. The FDA has approved the clinical application of two CAR-T cell therapies, Novartis and Kite. In Chinese Mainland, there are also as many as 214 CAR-T research units reported and registered in ClinicalTrials.gov. (as at 30 April 2019).

At present, most of the studies have focused on the specific targets of CD19 (or CD20, CD33, CD123, BCMA, etc.) and B cell malignancies, including leukemia, lymphoma and myeloma. In terms of solid tumors, the most important antigens were GPC3, mesothelin, epidermal growth factor receptor (EGFR) and EpCAM. Hpatic celluler cancer (HCC) is still the most studied solid tumor in Chinese Mainland. In the preliminary report of the CAR-T cell assay (NCT02541370) against CD133+ epithelial tumors, the number of CAR-T cells was negatively correlated with that of CD133+ epithelial cells. It has been reported that refractory bile duct cancer is treated by continuous injection of two different types of CAR-T cells targeting EGFR and CD133. These engineering T cells modified by CARs may be redirected to a single target, or also simultaneously/ sequentially double targets, even multiple targets. CAR-T cells targeting the T-cell-receptor/ antigenic-peptide complex and general CAR-T cells represent the two most recent directions in CAR-T cell research. More and more studies suggest that CAR-T cell therapy is becoming a mainstream cellular immunotherapy.

In the review, we summarized the CAR-T cell therapies that are undergoing clinical trials, and described the current research status of CAR-T technology in Chinese Mainland.

Regulation of gastrointestinal immune microenvironment and strategic exploration of novel cell therapy

胃腸道免疫微環境調控與新型細胞治療策略探索

Wen-Wei Hu

胡文蔚

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Gastrointestinal malignancies retain a high prevalence rate in China, accounting for the top five cancer morbidity and mortality. Surgery, radiotherapy, chemotherapy, targeted-therapy and immunotherapy have brought survival benefits to patients, but the field has yet to meet a breakthrough. Therefore, it is of great scientific significance to explore the regulation mechanism of gastrointestinal immune microenvironment and establish a precision diagnosis and treatment strategy accordingly .

Gastrointestinal tumor immune microenvironment has long been the focus of our basic research and clinical transformation at the Cancer Center of Changzhou First People's Hospital. The cancer center is equipped with tumor specific antigen screening, immune checkpoint monitoring, immune function analysis, oncogenetic diagnosis, new functional imaging technology and novel cell therapy technology, based on which we combine the concept of precision medicine with immunotherapy, and construct a precision diagnosis and treatment system for gastrointestinal tumors that benefits patients greatly. The system includes a new cell therapy strategy based on immune checkpoint intervention, research and application of inflammatory cytokines such as IL-33, IL-36γ in regulating anti-tumor immune response, and a systematic study using diffusion imaging, chemical shift imaging, blood oxygen level dependent imaging, magnetic sensitive imaging and other new functional imaging techniques to help preoperative diagnosis and micrometastasis detection.

Through systematic studies of the gastrointestinal immune microenvironment, we have constructed novel CAR-T cells expressing CEA or co-expressing CEA and IL-33, and conducted multi-center clinical studies on refractory gastrointestinal tumors. Using immune cell therapy, the cancer center is committed to benefiting gastrointestinal tumor patients with longer survival.

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亞太地區肝病合作研究論壇

Liver Forum for Collaborative Research in Asia-Pacific Region

協辦單位：臺北榮民總醫院國際醫療中心及胃腸肝膽科

時 間：108年6月22日 09:00~11:05
Time：June 22, 2019 09:00~11:05

地 點：台北國際會議中心 201C 會議室
Place：Conference Room 201C
Taipei International Convention Center

亞太地區肝病合作研究論壇

Liver Forum for Collaborative Research in Asia-Pacific Region

The current status of reimbursement criteria for liver diseases in Taiwan National Health System

臺灣肝臟疾病治療健保給付之現況

Pei-Chang Lee

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臺北榮民總醫院 內科部 胃腸肝膽科

Taiwan is an endemic area for hepatitis B and C. According to previous epidemiologic studies, 12% of the adult populations (approximately 2.5 million) are HBV carriers, and around 750,000 subjects (3% of general populations) have positive anti-HCV in sera. This would lead to liver cirrhosis and hepatocellular carcinoma in these patients and account for a great health burden in our society.

In the past decades, researchers and clinical physicians had explored the natural history, pathogenesis and the outcomes of chronic hepatitis, the risk stratification of developing cirrhosis or hepatoma as well as the appropriate anti-viral treatment, including interferon based therapy and nucleos(t)ide analogues.

Regarding to the treatment for chronic hepatitis C, it has entered into a new ear since the introduction of direct-acting anti-viral agents (DAAs). The patients were treated according to HCV genotype, clinical practice and reimbursement criteria of national health insurance program in Taiwan. A recent study showed that the overall sustained virological response rates at 12 weeks post-treatment were comparable with those in previous pivotal trials, and the safety profiles were acceptable. The detailed information about epidemiology, clinical problems and treatment issue will be discussed in the iver Forum for Collaborative Research in Asia-Pacific Region.

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榮總、三總、中研院合作研究成果發表會

VTA Joint Project Symposium

時 間：108年6月22日　　08:00~12:20
Time：June 22, 2019　　08:00~12:20

地 點：台北國際會議中心 201D 會議室
Place：Conference Room 201D
Taipei International Convention Center

榮總、三總、中研院合作研究成果發表會
VTA Joint Project Symposium

11-1 The pre-s2 deletion HBV mutants are responsible for the intracellular accumulation of the HBs protein, ER stress and mitochondria dysfunction ..... Yuh-Jin Liang

11-2 Evaluation of the therapeutic efficacy of a novel molecular chaperone ACK170 with GLA-IGF2 fusion enzyme in mouse model of Fabry disease ..... Dau-Ming Niu

11-3 The identification of mutant genes and clinical phenotypes in the patients with atrial fibrillation ..... Yu-Feng Hu

11-4 Development of circulating tumor cell cluster enrichment and analysis for the study of lung and upper aerodigestive cancers .....Ying-Chih Chang

11-5 To investigate the regulatory role of Blimp-1 in T cells and B cells in the pathogenesis of experimental autoimmune encephalomyelitis: Targeting on interleukin-21 and regulatory B cells..... Huey-Kang Sytwu

11-6 Metabolomic identification of lipid mediators as diagnostic biomarkers in humans with cardiovascular disease ..... Chin-Chou Huang

11-7 The Sirtuin 1 expression of peripheral blood mononuclear cells and endothelial progenitor cells in PAH .....Heng-Huei Lin

11-8 Vitamin D intake and gut microbiome expression in the patients with tubular adenoma and colorectal cancer ..... Ching-Liang Lu

11-9 Study the hydrolyzing activity of alkaline phosphatase on carbapenems and screen for carbapenemase inhibitor..... Jeffy Chern

11-10 Differential roles of abnormal O-glycosylation of IgA in the pathogenesis of IgA nephropathy .....Ann Chen

The pre-s2 deletion HBV mutants are responsible for the intracellular accumulation of the HBs protein, ER stress and mitochondria dysfunction

B 肝病毒 pre-s2 缺失的突變體影響細胞內病毒外套蛋白的積累、內質網應激和線粒體功能障礙

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Background: Pre-S deletion HBV mutants are associated with HCC development and postoperative recurrence. Mitochondrial is related to lipid metabolism, liver diseases and HCC development. This study aimed to investigate the association of wild type and pre-S2 deletion HBV mutants with HBsAg retention, ER stress and mitochondrial dysfunction.

Methods: The HBV whole genome expression plasmids containing wild type or various pre-S2 deletion mutant sequences under the driving of HBV endogenous promoter or CMV promoter were transfected into Huh7 cells. The intracellular retention of HBsAg and the subsequent ER stress or mitochondria dysfunction were compared between Huh-7 cells transfected by plasmids expressing wild type HBV or various pre-S2 deletion mutants and hepatocytes of HBV infected FRG mice containing chimeric human hepatocytes.

Results: The ratio of intracellular to the HBsAg in culture medium were calculated. Intracellular HBsAg retention ratio was the lowest in the wild type, followed by the pre-S2 mutant with proline 142, and the highest in the HBV pre-S2 mutant without proline. The ER stress markers (pIRE1α, XBP1, CHOP) were significantly higher in Huh-7 cells transfected with plasmids of pre-S2 mutants by immunoblotting analysis. Colocalizations of HBsAg and an ER-marker calnexin were confirmed by confocal microscopy. In contrast to the diffuse and homogenous distribution of HBsAg expressed by wild type HBV, pre-S2 deleted HBsAg located over perinuclear area and aggregated into coarse granules or clumps in both transfected Huh-7 cells and HBV-infected human hepatocytes in FRG mice. Electron micrographs revealed that aberrant ER ultra-structures include ER dilation and fragmentation in HBV expressing cells. In addition, mitochondria fragmented with defects in cristae shape were also found in both wild type and pre-S2 mutants HBV expressing cells with different extents under transmission electron microscopy. Time lapse live imaging of mitochondria labeled with MitoTracker revealed that the mitochondria motility were impaired in wild type HBV expressing cells and even more severe in pre-S2 mutants-expressing cells. Using the human liver chimeric mouse model of Fah/Rag2/Il2rg (FRG), serum HBV DNA levels of FRG mice infected by the pre-S2 deletion HBV mutant were 2 logs lower than those infected by the wild type. The secretion of HBsAg in the serum of FRG mice infected with the pre-S2 deletion HBV mutant was also decreased.

Conclusion: Pre-S2 deletion HBV mutants are impaired in secretion which resulted in the retention of HBsAg inside the liver cells. The intracellular accumulation of HBsAg induces ER stress, mitochondria dysfunction which may subsequently impair lipid metabolism and contribute to HCC development.

Evaluation of the therapeutic efficacy of a novel molecular chaperone ACK170 with GLA-IGF2 fusion enzyme in mouse model of Fabry disease

評估新穎化學伴護藥物 ACK170 輔助 GLA-IGF2 融合酵素對法布瑞氏症動物模式的治療成效

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臺北榮民總醫院 兒童醫學部 及 國立陽明大學 臨床醫學研究所

Background: Fabry disease is an X-linked inheritable lysosomal storage disease caused by genetic defects on α-galactosidase, which resulted in accumulation of globotriaosylceramide in the lysosomes and induced clinicopathological manifestations in heart, kidney and vessels. There is a surprising high incidence of cardiac Fabry disease harboring IVS4+919 G>A mutation in Taiwan and some patients have cardiac fibrosis progressive symptoms before hypertrophic cardiomyopathy. The treatment of Fabry disease is currently depended on enzyme replacement therapy (ERT), but the costs of ERT were extreme expensive and patients' quality of life of were significantly affected. Therefore, it is urgent to explore an alternative therapeutic strategy.

Methods: GLA enzyme activity was calculated by measuring the released of 4-MU which was determined by fluorescence measurement, while the amount of GLA is determined using western blot. Cellular and mitochondria ROS level is examined using DCFDA and mitoSOX staining. The amount of Gb3 is observed by Immunofluorescence assay.

Results: We demonstrated that the co-treatment of fusion protein GLA-IGF2 with ACK170 can significantly increase intracellular enzyme activity and effectively decrease the accumulated Gb3 in Fabry patient derived fibroblast. We also show that the GLA-IGF2 fusion protein can effectively reduce the cell damage and intracellular oxidative stress caused by the accumulation of Gb3.

Conclusion: We suspected that this pilot study may facilitate further investigation of the GLA-IGF2 fusion protein and pharmacological small molecule, such as ACK170, in the future

The identification of mutant genes and clinical phenotypes in the patients with atrial fibrillation

分析鑑定心房顫動的致病基因與其表現型

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Background: Atrial fibrillation (AF) is the most common arrhythmia with high morbidity and mortality. However, the medical treatment for AF has progressed slowly and is associated with signifcant side effects and pro-arrhythmias. Induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) can replicate electrophysiology patterns of human diseases and overcome inter-species differences from animal experimental models. This human cell model has been considered a translational system for drug discovery and mechanism study. To date, the iPSC-CMs with an AF phenotype is still underdeveloped.

Methods: The pathogenetic mutation was screened for the patients with familial early onset AF. The iPSCs were generated by reprogramming peripheral blood cells derived from these patients, and then were differentiated to iPSC-CMs. The calcium image and patch clamp were used to determine the clinically relevant phenotypes and compared to control iPSC-CMs.

Results: We performed whole exome sequence for the patients with early-onset AF and their family members, which revealed a novel mutation (uniparental disomy) in one of the patients. The genes within this mutation site regulate the splicing of the proteins and function in connection with the regulation of ion flux. We further preliminarily validated this mutation in the different population of AF patients. AF iPSC-CMs were successfully generated. The electrophysiology phenotypes were different between AF and control iPSC-CMs. The action potential durations of AF iPSC-CMs were comparable to those of control iPSC-CMs, but the recovery time of automaticity after burst electrical stimulation was longer in AF iPSC-CMs.

Conclusion: A human cardiomyocyte platform for AF was generated as a new disease model.

Development of circulating tumor cell cluster enrichment and analysis for the study of lung and upper aerodigestive cancers

設計並建立群循環腫瘤細胞濃縮及分析的流程並應用於呼吸器官癌症研究

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Background: Recent studies suggested that circulating tumor cell (CTC) clusters may have a higher capacity for initiating metastatic tumors than single CTCs. To facilitate the CTC research and eventually deploy it as a clinical tool, it is pivotal to develop a high-performance CTC capturing device that could capture both single and clustered CTCs efficiently. Here, we designed an antibody-dendrimer-conjugated lipid bilayer coating CTC platform (DS-Platform), aiming to improve the capture rate of low-expression EpCAM cancer (Chang, AS). Furthermore, CTC cluster dissemination mechanism in HNSCC patients (Yang, TVGH), as well as cohort study of CTCs and cfDNA in NSCLC patients (Chou, TVGH) were conducted.

Methods: The DS-Platform was designed, fabricated, and characterized. The spiked cancer cell lines with various EpCAM expression levels were spiked in whole blood for evaluation. CTCs were identified as panCK+/CD45-/DAPI+ in HNSCC, and TTF1-CK7+/CD45-/DAPI+ in NSCLC. The CTC clusters were defined as a cell cluster containing at least two or more cells, among which at least one of them was CTC.

Results: The DS-Platform showed a great improvement of capture efficiency for the low-expression antigen cell line. CTCs were collected from NSCLC (n=235) and HNSCC (n= 41) successfully and underwent IF, cell culture, and DNA analysis. Among them, CTCs and cluster counts (2mL peripheral blood) of NSCLC (n=106) prior to TKI treatments, and various stages of HNSCC (n = 28) were analyzed. CTC cluster counts correlated with the clinical stages of NSCLC (I & II vs. III & IV) but not the tumor size. In HNSCC, cluster counts correlate with the lymph node metastasis, recurrence and treatment response.

Conclusion: We have successfully developed DS-Platform and confirmed its application in capturing both CTCs and clustered CTCs with low-EpCAM expression levels. Clustered CTCs are better prognostic markers than the single CTCs in both NSCLC and HNSCC. Further analysis in cell viability, proliferation potential, and mutation incidence are undergoing.

To investigate the regulatory role of Blimp-1 in T cells and B cells in the pathogenesis of experimental autoimmune encephalomyelitis: Targeting on interleukin-21 and regulatory B cells

研究 Blimp-1 如何透過調控 T 及 B 淋巴細胞來影響實驗性自體免疫腦脊髓炎的致病過程：聚焦在介白質 21 及調節性 B 淋巴細胞的創新研究

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三軍總醫院 醫學研究室

Background: Current reports have demonstrated that B lymphocyte-induced maturation protein 1 (Blimp-1) expands its control over T cells and is associated with susceptibility to colitis in C57BL/6 mice and autoimmune diabetes in non-obese diabetic (NOD) mice with Blimp-1 deficiency. In this grant proposal, we elucidated the transcriptional regulation of Blimp-1 in pathogenic cytokine IL-21 and IL-10 production and its subsequent effect on encephalomyelitogenesis.

Methods: To dissect the pathogenic feature on encephalomyelitogenic property of Blimp-$1^{flox/flow}$/Lck^{Cre+} T and Blimp-$1^{flox/flow}$/$CD19^{Cre+}$ B cells, we will characterize the cytokine profiles and differentiation of those "pathogenic" T and B cells. We have elucidated the potential molecular interaction between Blimp-1 and other transcriptional factors in transcriptionally regulating the cytokine IL-21 and IL-10 production.

Results: First**,** ChIP results proven that Blimp-1 bound to Il21 promoter in control WT CD4 T cells, and blockade of IL-21 attenuated Blimp-1 deficiency-mediated colitis. Moreover, our results showed that Blimp-1 attenuates c-Maf-IL-21 axis in CD4 T cells. In B cell study, our results showed that Blimp-1 negatively regulates the generation of B10 cells and IL-10 production by B10 cells. Our data revealed that mice lacking Blimp-1 in B cells may worsen the development of EAE, despite that more Breg cells and IL-10 were produced.

Conclusion: We demonstrate that Blimp-1 negatively regulates c-Maf-dependent IL-21 production in CD4 T cells and positively modulates IL-10 expression in B10 cells. Furthermore, molecular mechanism mediated by Blimp-1 might be a potential therapeutic target for autoimmune diseases.

Metabolomic identification of lipid mediators as diagnostic biomarkers in humans with cardiovascular disease

由脂質代謝體辨識人類心血管疾病的診斷性生化指標

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Background: Polyunsaturated fatty acids (PUFAs) are thought to be beneficial to cardiovascular health. This study aimed to investigate the prognostic impacts of the PUFA metabolites, oxylipins, on clinical outcomes in patients with cardiovascular disease, including stable coronary artery disease (CAD) and hypertension.

Methods: A total of patients with stable CAD and hypertension were prospectively followed up. Among them, patients with new onset of acute myocardial infarction (AMI) during follow-up were studied. Age- and gender-matched patients without any cardiovascular event during follow-up were studied for control.

Results: The incidence of future AMI was significantly increased in CAD patients with higher baseline serum levels of specific arachidonic acid metabolites when compared to their counterparts. Serum levels of these specific arachidonic acid metabolites were positively correlated to that of tumor necrosis factor-α and N-terminal pro B-type natriuretic peptide.

Conclusion: Serum specific oxylipins levels were increased at baseline and associated with future onset of AMI, suggesting their novel role for secondary prevention in stable CAD patients.

The Sirtuin 1 expression of peripheral blood mononuclear cells and endothelial progenitor cells in PAH

肺動脈高壓病患的去乙醯化酶 (Sirt1) 的活性及表現

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Background: Pulmonary arterial hypertension (PAH) is a progressive disease characterized by endothelial dysfunction, excessive proliferation and impaired apoptosis of vascular smooth muscle cells, and refractory vasoconstriction. The endothelial progenitor cells may become a promising therapeutic option in pulmonary arterial hypertension, however, understanding the molecular sequelae is urgently needed before applying this novel therapy. SIRT1, a class III histone deacetylase, plays an important role in improving EPCs function. Hence, we would like to explore the Sirt1 and associated proteins expression of endothelial progenitor cells in patients with PAH.

Methods: To compare the expression level of Sirt1 and senescence-associated markers in EPCs, the human peripheral blood-derived EPCs were examined by immunoblotting analysis. Determination of EPCs biological function, cell proliferation, cell migration and tube formation were examined. To evaluate the Sirt1 decrease the EPCs senescence and promote the endothelial repair, EPCs overexpression Sirt1 and infused with PAH mice.

Results: We found that EPCs from normal populations with higher expression of Sirt1, P16 and P21 than those from PAH patients. We also found that the ability of tube formation was decreased in the EPCs of PAH patients. Immunofluorescence results shown that PAH mice infused with human EPC could repair the endothelial cell in lung artery. We used the Ad-Sirt1 to over expression the EPCs of PAH patients because of Sirt1 associated with angiogenesis and found that PAH patients' EPCs with overexpression of Sirt1 could improve high PA pressure than PAH patients' EPCs without Sirt1 manipulation.

Conclusion: In this study, we demonstrate that sirt1 regulate the aging gene and promoting angiogenesis in PAH mice. Sirt1 may play an important role in EPCs therapy for pulmonary arterial hypertension.

Vitamin D intake and gut microbiome expression in the patients with tubular adenoma and colorectal cancer

維生素 D 攝取與腸道菌相表現在大腸腺瘤及大腸癌患者之研究

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Background: Colorectal carcinoma (CRC) is the 3rd highest cancer incidence in the world. Genetic changes with tubular adenoma (TA) can progress to CRC, a process known as the adenoma-carcinoma sequence. Gut microbiota has recently been demonstrated to be another important player in the CRC carcinogenesis. Vitamin D is converted into its active form calcitriol and binds to the vitamin D receptor (VDR), which functions as a transcription factor to regulate various biological processes including cellular differentiation, immune response, and carcinoma inhibition. Gut microbiota would interact with VDR and lead to alterations in gut inflammation, which would also contribute to carcinogenesis. In this study, we hypothesize that different gut microbiome ecology is present among healthy control, patients with tubular adenoma (TA) and CRC.

Methods: A validated semiquantitative food frequency questionnaire (FFQ) was administered to assess dietary intake. Serum levels of vitamin D and gut VDR expression were examined by enzyme-linked immunosorbent assay and immunohistochemistry analysis. Gut microbiome using full-length 16s rRNA amplicon sequencing.

Results: In this study, we found that there seemed to be no significant difference in the total calorie, protein, fiber or vitamin D intake between 3 groups**.** The diversity of stool microbial communities and gut VDR expression of subjects with TA and SSA was marginally lower than controls.

Conclusion: Different gut microbiota and gut VDR expression could contribute to distinct pathway for formation of TA and SSA.

Study the hydrolyzing activity of alkaline phosphatase on carbapenems and screen for carbapenemase inhibitor

鹼性磷酸酶對碳青黴烯水解作用之化學結構變化、臨床重要性、治療策略及篩選潛在的水解酶抑制劑之研究

Jeffy Chern

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Background: Alkaline phosphatases (ALP) widely exist in many organisms. In clinical practice, the ALP level detected from bloodstream serves as a diagnostically important indicator. Using motif-mapping, we unraveled an additional functional motif of ALP- a class B β-lactamase-like motif. However, little is known about the interplay between ALP and β-lactam antibiotics. Herein, we investigated the molecular mechanism underlying human ALP-mediated meropenem degradation and its role in patients with high ALP.

Methods: To map class B β-lactamase-like domain in ALP, molecular dynamic calculation was conducted. To establish the interplay between meropenem and human ALP, human ALP was purified and characterized. To demonstrate meropenem underwent human ALP-dependent degradation, tandem mass spectrometry and NMR spectroscopy methodologies were developed. To clarify the role of ALP in clinical practice, patients' blood samples with different status of ALP were examined.

Results: We unraveled that meropenem directly underwent ALP-mediated hydrolysis in a metallo-catalyzed manner. The coordination of the zinc in ALP served as the prerequisite for meropenem degradation. The comprehensive screenings of other ALP-susceptible β-lactams and patients' blood-directed assays are still under investigation and development.

Conclusion: We demonstrate that ALP functions as a β-lactam hydrolyzer through metallo-catalysis. Further pharmacokinetic investigation of the given β-lactams in particular ALP status patients remain to be examined. If the administrated β-lactam undergoes ALP degradation, the precaution should be taken into consideration when prescribing β-lactam to patients with high ALP.

Differential roles of abnormal O-glycosylation of IgA in the pathogenesis of IgA nephropathy

異常 O- 聯結醣基化 IgA 於 IgA 腎病變之致病機制之鑑別角色

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Background: IgA nephropathy (IgAN) is the most common glomerular disorder worldwide. Recently, IgAN has been considered to be an autoimmune disease resulting from glomerular nephritogenic immune complexes (ICs) containing galactose-deficient IgA1 (as autoantigen) bound by IgG anti-glycan autoantibodies. However, the exact pathogenic role of the abnormal O-glycosylation of IgA molecules and related molecular pathways in this renal disorder has yet to be determined. The purpose of this proposal was to determine the differential roles of abnormal O-glycosylation of IgA molecules in the pathogenesis of IgAN. The ultimate goal is to establish a glycan-based personalized medicine and early diagnosis for IgAN in the very near future.

Methods: In order to generate the humanized mouse IgA (h-mIgA), we generated two CRISPR/Cas9 plasmids targeting upstream and downstream of mIgA hinge region, and one knock-in plasmid carry the hinge region sequence of human IgA. We used ELISA binding assays with various Gd-IgA binding reagents to investigate the O-glycosylation levels of IgA from IgAN patients' serum. The impact of glycosylation levels of IgA molecule in the distribution and clearance/elimination of IgA and IgA ICs in vivo was determined by direct counting and autoradiography at light microscopy and level has been performed in mice, using isotope-labeling technique (I125 isotopes).

Results: In this project we generated a humanized hinge regin of IgA in a mouse IgA (h-mIgA) using CRISPR/Cas9-modified TEPC-15 hybridoma. We further generated the h-mIgA without O-glycosylation (h-mIgA-NG) by deleting the C1galt1 gene by CRISPR/Cas9 in the h-mIgA-producing TEPC-15 hybridoma. In addition, we analyzed the O-glycosylation levels of IgA in the serum from IgAN patients and normal subjects (the human samples provided by sub-project 2) by ELISA-based binding assays. We completed distribution and clearance/elimination of abnormaly glycosylated IgA1 in vivo.

Conclusion: After completion of the integrated project, we achieved the following goals: 1. Establishment a humanized hinge region of TPEC-15 hybridoma; 2. Galactose-deficient IgA1 deposition in renal tissues with IgAN; 3. Abnormal glycosylation of IgA1 played a role in the pathogenesis of IgAN.

The pathogenic role of hepatitis C virus in rheumatic disease

C 型肝炎病毒在免疫風濕疾病之致病角色

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Background: Several studies observed that rituximab (RTX) may enhance hepatitis C virus (HCV) viral activity. MicroRNAs (miRNAs) have been implicated in modulating host immune response in HCV infection and then shuttled by the exosomes to exert biological functions. But the role of exosomal miRNAs in RTX-related HCV activity enhancement remains unclear.

Methods: The association between RTX and increased HCV activity was examined using an *in vitro* cell-based assay. The purified exosomes were confirmed using immunoblotting, flow cytometry and quantified using enzyme-linked immunosorbent assay. Exosomal miRNA-155 (exo-miR-155) levels were measured using quantitative reverse transcription PCR.

Results: *In vitro* data showed that B cell–derived miR-155 could inhibit HCV replication in hepatocytes through exosome transmission. Rituximab could both induce B cell depletion and affect the intracellular miR-155 production as well as exo-miR-155 transmission, and then enhance HCV activity in hepatocytes (P<0.005). Increased serum exosome levels in rheumatoid arthritis (RA) patients with HCV infection compared with those without infection (P<0.01). The exo-miR-155 levels were significantly increased in RA patients with HCV infection compared with those without infection (3.13±1.09 vs. 1.00±0.19 fold, P<0.01). A significantly greater decrement of the exo-miR-155 expression was observed after RTX therapy compared with those before therapy (0.52±0.03 vs. 1.00±0.08 fold, P<0.01), and HCV viral loads increased simultaneously (2.32×10^7 vs. 1.79×10^5 IU/ml, P<0.05).

Conclusion: The circulating exo-miR-155 levels were negatively correlated with HCV viral loads and subsequently associated with RTX-related HCV activity enhancement in RA patients; exo-miR-155 may become a potential diagnostic biomarker or therapeutic target.

Development of biomarkers for Huntington's disease

亨丁頓氏症生物標誌之研究

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Background: Huntington's disease (HD) is a neurodegenerative disorder caused by the CAG expansion in the exon1 of huntingtin (*htt*). The disease-causing, polyQ-expanded Huntingtin protein (i.e., mHTT) exists in many tissues with the highest level in the brain. No effective treatment to delay the disease onset or retard the disease progression is currently available due to the lack of robust and feasible biomarkers. The goal of the present study was to investigate whether accumulation of soluble mHTT oligomers in peripheral blood may serve as a reliable biomarker for the onset and progression of HD.

Methods: At present, the most reliable measures to assess the progression of HD include the Unified Huntington's Disease Rating Scale and magnetic resonance imaging (MRI), which usually take at least one year to observe disease progression. mHTT has been reported to exist in the brain, multiple peripheral tissues, and blood cells. Based on an anti-oligomeric mHTT antibody (Habe1), several classical approaches and two recently developed technologies (e.g., immunomagnetic reduction assay, single-molecule arrays, and classical ELISA) were used to monitor the levels of soluble mHTT oligomers in the blood, which were also used to correlate with the volume of two brain areas of HD patients.

Results: We found that 1) Habe1 recognized the progressive accumulation of oligomeric and aggregate forms of mHTT in the brain and peripheral blood cells of HD mice (R6/2); 2) Habe1 recognized the oligomeric mHTT in human peripheral blood (PBMCs and plasma) of preHD and HD patients; 3) the level of oligomeric mHTT was altered in human peripheral blood (PBMCs and plasma) during disease progression.

Conclusion: Our results suggest that Habe1 has the potential to serve as a powerful tool to monitor oligomeric mHTT and might be used as a sensitive biomarker for HD progression.

Investigation of the utility of Crispr/cas9 gene-editing in correction the hereditary retinal disease models by 3D organoid-iPSC system

探討 CRISPR/CAS9 基因修飾在 3D 立體類器官視網膜遺傳性病變之功能性編譯

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Background: Retinal degeneration and dystrophies severely affect vision and cause blindness and are often characterized by dysfunctions of photoreceptor and/or retinal pigment epithelium cell layers of the retina. The photoreceptor is known to be a specialized primary cilium and mutations of retinal disorders are often found in proteins of the connecting cilium (CC) and the periciliary complex (PCC) of photoreceptors, which is important for maintaining proper functions of photoreceptor. Despite the clinical importance of these proteins, their relative localization is largely unknown due to the small characteristic lengths when comparing with the diffraction limit of light. Furthermore, molecular aberrations in mutant photoreceptors remain elusive, due to the difficulty of obtaining patient-specific photoreceptors. The gene responsible for X-linked juvenile retinoschisis (XLRS) was RS1 which encodes a secreted extracellular protein called retinoschisin or RS1. To date, more than 190 RS1 mutations were identified, most of them locate in the discodin domain of retinoschisin which causes endoplasmic reticulum retention of RS1 protein. However, the molecular mechanism and therapeutic method of mutated RS1 in XLRS is still elusive.

Methods: We reveal the pathogenesis pathways of XLRS and to establish a gene therapy method to overcome the mutated RS1 gene in XLRS. We use patient-specific inducible pluripotent cells (iPSCs) to reconstitute an *in vitro* disease model of XLRS to explore the mechanism and effect of RS1 mutation on human retina. We apply CRISPR-CAS9 gene correction technique to develop gene correction platform targeting the mutated RS1 gene in XLRS. With the nano-technique, we develop a RS1 gene therapy method that can be delivered into retina and specifically repair the mutated RS1 gene.

Results: (1) Establish patient-specific iPSCs from patients with XLRS hereditary retinal dystrophy and differentiate the iPSC into multilayered optic cup structure. (2) Understanding the pathophysiological mechanism of retina degeneration using the platform of patient-specific hiPSC-derived photoreceptors and 3D-retina. (3) Development of CRISPR/CAS9 gene correction of RS-1 mutation in 3D OV.

Conclusion: We show humanized rat by injecting XLRS-iPSC-derived OVs in immunocompromised rat. The animal model were serve as an in vivo drug screening platform to investigate and identify novel XLRS treatments.

Role of galectin-1 in the development of abdominal aortic aneurysm

半乳糖凝集素 -1 在腹主動脈瘤致病過程中之角色

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Background: Abdominal aortic aneurysm (AAA) is a common vascular disease that causes asymptomatic rupture of aorta and significant mortality in aged subjects. The pathological features of AAA include the degradation and fragmentation of elastin/collagen, loss of medial vascular smooth muscle cells (VSMCs), and chronic adventitial inflammation. Nevertheless, the detailed mechanism underlying AAA development is not completely understood. Galectin-1 (Gal-1) is a prototype galectin expressed on vascular cells with β-galactoside-binding activity. Given that Gal-1 influences many biological processes, whether it has a role in AAA remains to be established.

Methods: ApoE-knockout (KO) and apoE/Gal-1-double knockout (dKO) mice were subjected to angiotensin II (Ang II) infusion for 4 weeks. The incidence and severity of AAA developed were assessed by ultrasonography and patho-histological examination. The level of Gal-1 in sera of animals and human patients was measured by ELISA. The expression of matrix metalloproteases (MMPs) in aortic tissues and cultured VSMCs and adventitial fibroblasts was examined by zymography and Western blot analysis.

Results: Serum Gal-1 was highly elevated in Ang II-infused apoE-KO mice. The incidence and severity of AAA associated with aortic MMPs induction following Ang II infusion were much reduced in apoE/Gal-1-dKO mice comparing to apoE-KO mice. Gal-1 was upregulated in VSMCs and adventitial fibroblasts following TNF-α treatment. Furthermore, TNF-α induced transient Erk phosphorylation and MMP-9 expression were much lower in Gal-1-KO fibroblasts comparing to wild type cells. Given that Gal-1 is susceptible to oxidation, the effect of oxidized Gal-1 (oxGal-1) on MMP expression was also examined. It was shown that oxGal-1, but not the redox-insensitive Gal-1, induced MMP-9 expression in both VSMCs and fibroblasts. Further study showed that the serum level of Gal-1 in AAA patients was significantly higher than that of control subjects.

Conclusion: Gal-1 is upregulated by inflammatory cytokine and implicated in the modulation of MMP expression and medial degeneration during the course of AAA development.

Diagnosis and monitoring delayed onset hereditary deafness study

遲發型遺傳性聽損病因探討與聽力監測模式之研究

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Background: Sensorineural hearing loss (SNHL) is the most common congenital disability and sensory disorder in humans. In the developed countries, it is estimated that SNHL can be attributed to genetic factors in over 2/3 of affected children, i.e., hereditary deafness, GJB2 and SLC26A4 gene variants are the most common causes of for hereditary deafness. The degree of hearing impairment caused by SLC26A4 or GJB2 variants ranges from mild to profound SNHL. The onset of hearing loss also varies; it can be early onset (detected by newborn hearing test at birth) or delayed-onset (happening at teenage SNHL. For the delayed-onset SNHL caused by SLC26A4 and GJB2 variants, even though the hearing pattern could be fluctuating, prevention or slowing down the hearing loss progression is possible with close hearing monitoring and proper prevention.

Methods: Pure tone audiometry is the gold standard to evaluate the hearing level. However, it has to be performed in a sound-proof room by hearing professionals. Therefore, it is not easily accessible and makes daily hearing monitoring difficult for the patients. To solve this main problem, our research team has developed a smartphone-based application “Ear Scale App”, which contains four test tones with adjacent hearing scales differ from each other by 5 dB, ranging from 1dBHL (S1) to 96 dB HL (S20), making it possible for these patients to monitor and report their hearing level. We also established the diagnostic gene test for the SLC26A4 and GJB2 variants by next-generation sequencing.

Results: We incorporated the NGS-based genetic testing and “Ear Scale App” hearing monitoring system to actively preserve the hearing level of delayed-onset genetic deafness patients caused by the common SLC26A4 and GJB2 gene variants. We found 21 cases, including 8 cases of SLC26A4 variants and 13 cases of GJB2 variants, are sequenced and confirmed by NGS. For the 21 sequenced cases of delayed-onset genetic deafness, we monitored the patient’s hearing level by the “Ear Scale App.”

Conclusion: Using the smartphone-based hearing test system is a feasible way to monitor hearing level change for the delayed-onset genetic deafness patients caused by SLC26A4 and GJB2 variants.

Investigating the role of Meta1-mediated GPCR network in cancer metastasis evolution through CRISPR-Cas9 genomic editing

利用 CRISPR-Cas9 基因編輯研究 Meta1 引導 GPCR 訊息傳導網絡在癌症轉移演化上扮演之角色

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Background: Cancer metastasis is one of the most devastating and world-wide clinical unmet needs. Cancer metastasis is an exceedingly complex and evolutionary process, in which cancer cells spread, through a series of sequential steps, from the tumor of origin to colonize distant organs. The identification of drivers of metastasis presents a unique challenge due to the heterogeneity of cancer.

Methods: In order to uncover the common candidate metastasis drivers from cancer heterogeneity, we used unbiased bioinformatics approaches by integrating cancer genomic data with clinical characters in patients. The functional validation of potential drivers responsible for metastasis has been performed through in vitro and in vivo experiments.

Results: We identified cancer cells that expressed a novel gene, *Meta1*, which encodes for a previously uncharacterized G protein-coupled receptor. Meta1, together with its interacting protein Int-X, autonomously expressed the ligand LigZ and mediated cancer metastasis in multiple cancer types. LigX-Meta1-Int-X GPCR signaling networks promoted cancer cell invasion *in vitro* and metastasis *in vivo*. Without a ligand, Meta1 activated Gaq and RhoA-GTP. Upon LigZ binding, downstream signaling of Meta1 extended to Gβγ activation and cAMP signaling, which led to cytoskeletal rearrangement and enhanced metastasis. In the presence of Meta1, Int-X interacted with Gβγ and enabled cancer cells to induce LigZ synthesis and activate metastasis-related genomic signatures through binding to Meta1 as the autocrine receptor. Primary tumors that expressed both Meta1 and Int-X in various cancer types correlated to worse metastasis-free survival in patients.

Conclusion: Our study identified LigX-Meta1-Int-X, a GPCR autocrine signaling pathway, prevalently involved in driving metastasis of different cancer types. Although the Meta1 autocrine signaling pathway has emerged from cancer heterogeneity and evolution, whether this pathway can serve as a common actionable target for the validation of predictive and prognostic biomarkers and for the development of preventive and treatment therapeutics merits for further investigation.

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2019輻射醫療處置國際研討會

Internal Symposium of Radiation Emergency Management

時 間：108年6月22日 08:00~12:00

Time：June 22, 2019 08:00~12:00

地 點：台北國際會議中心 201E 會議室

Place：Conference Room 201E
Taipei International Convention Center

2019輻射醫療處置國際研討會
Internal Symposium of Radiation Emergency Management

Applications of internal radiation dosimetry

體內輻射吸收劑量評估之應用

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Internal dosimetry deals with the determination of the amount and distribution of radiation energy deposited in tissue by radionuclides within the body. Nuclear medicine has been largely a diagnostic specialty, and model-derived average organ dose estimates for risk assessment. With the increasing therapeutic application of internal radionuclides and the need for greater accuracy, radiation dosimetry in nuclear medicine is evolving from population- and organ-average to patient- and position-specific dose estimation. In this study, we will discuss the importance of the history of radiation exposures and the current acceptable limits of this exposure for both personnel and patients, and this review will also discuss how to evaluate these exposures.

Radiation emergency medical management system in Taiwan: Role of regional emergency medical operation center, Ministry of Health and Welfare

台灣輻射災害緊急醫療體系管理：衛福部區域緊急醫療應變中心的角色

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輻射災害在醫療體系中是相當少見的災害，然而核輻射的應用在台灣的工業界和醫療界仍佔有重要的一席之地。相對於其他災害應變，輻射災害的應變與傷患處置對於從事緊急醫療救護的醫護人員是較不熟悉的領域。

衛生福利部依據緊急醫療救護法第九條，委託醫療機構於各區域內總成緊急醫療應變中心，即時監控區域內災害有關緊急醫療之事件，掌握區域內緊急醫療資訊及資源狀況，並定期辦理年度重大災害有關緊急醫療之演練及於跨直轄市、縣（市）之災害發生時，協助中央衛生主管機關調度區域內緊急醫療資源，進行應變工作。

輻射災害的相關醫療人員的教育訓練，以及各急救責任醫院的年度演習評核也是其中重要的一環。區域緊急應變中心藉由舉辦輻傷處置教育訓練活動，加強區域內醫護應變人員對於輻射傷患的處置能力，並以演習評核的方式，驗證教育訓練的成果，以備萬一發生輻射災害時，各級醫療應變人員能發揮專業訓練的成果，減少輻射災害所帶來的人命及健康衝擊。

Radiation emergency management in Taiwan: Experience in VGHTPE

台灣輻射醫療處置：臺北榮總經驗

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VGHTPE had been close co-operating with Tai-Power company since 1977 when Radiation Medicine Center was established.

Initially, our job was Annaly health exam, radiation injury patient care and emergency medical support for nuclear power plant. After two decades, New VGHTPE is tertiary duty hospital in radiation emergency program by the Department of Health, Executive Yuan. There is mainly three mission set for tertiary duty hospital, advance medical care for radiation injury patient, international cooperation and interchange for medical practice, radiation emergency training and exercise.

In Taiwan, more than 30k General License Uses of Nuclear Materials were issued. Injury from misconduct might have happened from time to time. In Taiwan, when having radiation emergency exercise, we much focus on accident from a nuclear power plant or accident from transporting radiation materials.

A team from VGHTPE went abroad for international cooperation and academic interchange. For example, NIRS, NAGASAKI university, and Fukushima prefecture in JAPAN, KIRAMs, NREMC in Korea. Also, Trainee from ED and NM went to in NIRS annually who brought the latest update globally.

Radiation emergency management (REM) in south Taiwan: Role of KMUH from past to future

高雄醫學大學附設中和紀念醫院在南臺灣輻射醫療處置之角色：從過去到未來

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Issue of radiation emergency management (REM) began in Taiwan since 25 years ago, due to medical support build-up for nuclear power plants. Kaohsiung Medical University Hospital (KMUH) is the oldest and famous medical center in Kaohsiung city 60 years ago. Therefore, former principal Tasi (President Tsai Juei-Hsiung) of Kaohsiung medical university, took responsibility for government appointment to construct the radiation emergency medical system to assistant the Maanshan nuclear power plant at Kenting, south Taiwan. During the past period times, special ward of hardware, training programs of education, medical staff exercises, advanced medical treatment, and even research were started on. From millennium, issue of REM is not only limited to nuclear power plant, but also industrial application, dirty bomb terrorist incidents, radionuclide transportation, and communication of foreign countries with nuclear devices. Our ministry of health and welfare reconstruct organizational structure with third grades and ten hospitals join programs in the Pintung county and Kaohsiung city. Kaohsiung Medical University Hospital (KMUH) is one of third medical centers for issues of REM in the third-grade hospitals at Kaohsiung city. Base on school of medicine, KMUH is still foundation of REM issue in the south Taiwan.

Recovery effects from the nuclear disaster

核災的恢復效應

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After the accident at Fukushima Daiichi Nuclear Power Station (FDNPS) in March 2011, Kawauchi village evacuated to Koriyama city. In December 2011, Nagasaki University started to support the recovery efforts of Kawauchi village by monitoring and evaluating environmental decontamination and communicating the risks with residents. In January 2012, Mr. Yuko Endo, the mayor of the village, declared his intention that the village office would return to their home town, and then achieved this by in March 2012. In May 2012, a public nurse of Nagasaki University was sent to Kawauchi to start communicating radiation health risks with residents. Simultaneously, we identified factors associated with "intention to return (ITR) to the village" in residents for the effective communication of risk.

In April 2013, a satellite office of Nagasaki University was opened in Kawauchi village and we supported the recovery efforts of the village through the evaluation of external and internal radiation exposure doses and communicated these risks with residents based on their exposure doses. We also supported the health promotion policy of the village by participating in health events in the village. We contributed to the lifting of the evacuation zone in the village by predicting exposure doses in residents who returned to the area after the evacuation order was rescinded. By April 2018, almost 81% of residents had returned to the village. Kawauchi village is now considered to be a "model case" of a community that recovered after the nuclear disaster.

Tomioka town is located within 10–20 km of the FDNPS. Immediately following the accident, almost all residents of Tomioka were forced to evacuate from their hometown to other areas, mainly Iwaki city and Koriyama city. Tomioka town was severely damaged by the earthquake and tsunami and was contaminated by radionuclides. After the situation stabilized following the accident, Tomioka's town office led the infrastructure recovery efforts and the tedious decontamination to remove radiocesium fallout in all areas except the "difficult-to-return-zone." On April 1, 2017, the Japanese government lifted the evacuation order for Tomioka; however, the number of residents who have returned to their homes remains limited.

Nagasaki University started the support of the recovery efforts of Tomioka town by monitoring and evaluating environmental decontamination and communicating these risks with residents from October 2016 onwards. In April 2017, we launched a satellite office in Tomioka's town office and communicated risk issues with residents who returned to the town, based on an evaluation of their external and internal exposure doses.

We also identified the factors that influenced the ITR of residents of Tomioka town. We revealed that being male, living with children under 18 years of age, usefulness of shopping facilities in Tomioka, reluctance to drink tap water, anxiety for the genetic effects of radiation exposure in the next generation, and requests for individual consultation with experts in health effects of radiation were associated with ITR.

Eight years have passed since the accident at the FDNPS, but the recovery of affected areas is still ongoing. Scientists should continue to cooperate with residents and local authorities to ensure the recovery of communities from the nuclear disaster, as the cooperation really started back in 2011.

Radiation emergency management experience in KIRAMS

輻射醫療處置：KIRAMS 經驗

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The presentation aims to introduce the activities by KIRAMS (Korea Institute of Radiological and Medical Sciences) – NREMC (National Radiation Emergency Medical Center) to strengthen medical preparedness and response to radiation emergencies in Korea.

After the Fukushima Daiichi nuclear power plant accident, the public fear about radiation has dramatically soared in Korea. In line with this concern, the Nuclear Safety and Security Commission (NSSC) was established in 2011 as a national authority for nuclear safety and regulation. KIRAMS-NREMC entrusted by NSSC, oversees medical aspects in responding to a radiation emergency. It operates the national radiation emergency medical network consisting of 12 primary hospitals and 12 secondary hospitals. It acts as a control tower to manage these 24 hospitals by allocating budget, distributing equipment and providing education and training to medical staffs and first responders. In addition, KIRAMS conducts dose assessments of radiation exposure with high level of accuracy and implements R&D programs for developing radiation injury therapeutics and evaluating low-dose radiation risks in daily life.

KIRAMS also engages in many activities to raise public awareness on radiation. KIRAMS has operated the Radiation Effect Clinic since 2011, which is the only clinic in Korea specialized in radiation injury. It provides the public with consultation on radiation health concerns, receives radiation accident reports through its 24/7 hotline (+82-1522-2300), and conducts regular health check-ups for occupational workers. In addition, KIRAMS offers classes on radiation basics and radiation protection to the elementary and middle schools near nuclear power plants.

Based on these activities, the presentation also illustrates an example of consulting a nation-wide public fear on radiation. Commonly called as radioactive mattress scandal, the event started with a Korean TV station's report on 3 May 2018 that some mattresses from a domestic manufacturer emit radioactive gas above safety standard. Consumers panicked with fear and the KIRAMS hotline started to be flooded with inquires. KIRAMS was one of the only sources which could provide accurate medical information to the public, and offered guidance that only lung cancer has been proven to be linked to radon exposure so far. By disseminating correct medical information amid chaos, KIRAMS acted as an opinion leader and contributed to alleviating the public's excessive fear.

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肺癌精準化治療的趨勢

Toward Precision Treatment of Lung Cancer

時 間：108年6月22日 08:00~11:50

Time：June 22, 2019 08:00~11:50

地 點：台北國際會議中心 201F 會議室

Place：Conference Room 201F
Taipei International Convention Center

肺癌精準化治療的趨勢
Toward Precision Treatment of Lung Cancer

Current treatment landscape and future trends for NSCLC

非小細胞肺癌的治療新趨勢

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Due to rapid changes and advancements for the clinical development in non-small cell lung cancer (NSCLC) treatment, treatment paradigm has become more and more complex.

The breakthrough development of first-, second- and third-generation of epidermal growth factor (EGFR) tyrosine kinase inhibitors, anaplastic lymphoma kinase (ALK) inhibitors, as well as agents targeting ROS-1 and BRAF mutations, has dramatically changed the guidelines to reflect the importance of molecular profiling. The availability of checkpoint inhibitors has also been heavily investigated in various lines of treatment settings for NSCLC. These immunotherapies may present a chance to provide a much more durable and superior outcomes as compared with traditional chemotherapies. Not only in monotherapy, the advancement of immunotherapies opens up numerous combinational possibilities, such as immunotherapy plus immunotherapy, immunotherapy plus chemotherapy, or even based on recent clinical data, immunotherapy plus anti-VEGF and chemotherapy.

This particular session summarizes the major shifts in the treatment of non-small cell lung cancer landscape over the past few years, specifically aiming to discuss the current treatment approaches for EGFR/ALK, ROS-1, BRAF mutated NSCLC, as well as the difference between non-squamous and squamous populations, and what upcoming changes we could expect in near future. The concept of precision medicine and the importance of molecular testing (such as next-generation sequencing) will also be briefly discussed.

Combination immunotherapy in NSCLC

非小細胞肺癌之免疫合併治療

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Immunotherapy has risen to 1st line treatment in metastatic non-small cell lung cancer. Unlike traditional cytotoxic chemotherapy and radiation therapy, clinicians have yet to gain familiarity with this new mode of treatment. Not all patients can benefit from immunotherapy at present time. In fact, we do not have reliable predictive markers yet. Scientists have started to try combining immunotherapy with other therapies in the hope of increasing clinical response.

Combination immunotherapy with cytotoxic chemotherapy is a viable option. Examples include pembrolizumab and atezolizumab which have both been combined with cytotoxic chemotherapy and achieved better PFS and OS than chemotherapy alone, even in low or negative PD-L1 expression populations.

Immunotherapy can also be combined with radiation therapy, such as in the PACIFIC study. Timing may be important. The shorter the time interval between the two therapies, the better the outcome.

PD-1/PD-L1 inhibitor combined with EGFR TKI trials are ongoing. Early results showed that EGFR TKI administration may increase response to immunotherapy in some patients. Data are not mature yet, however.

Immunotherapy + immunotherapy is also an option. The PD-1/CTLA-4 combination targets different “checkpoints” in cancer formation. This combination is non-redundant in theory. An example of such combination is the combo of nivolumab + ipilimumab, which have shown encouraging results in the Checkmate-227 study. Data from the TMB-high population of the trial have been published.

Current treatment landscape and future trends for small cell lung cancer

小細胞肺癌的治療新趨勢

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Small cell lung cancer (SCLC) remains an aggressive, deadly cancer with only modest effect on survival from standard chemotherapy. In contrast to lung adenocarcinoma, which includes several effective targeted therapies against different driver oncogenes, SCLC is still approached clinically as a single disease entity. However, with the advent of immunotherapy and comprehensive genomic and transcriptomic profiling, multiple new targets are showing promising results.

The addition of the anti-PDL1 antibody atezolizumab to chemotherapy provided a significant improvement in overall survival and progression free survival, compared with carboplatin and etoposide alone. Noteworthily, only 12.6% of patients remained progression-free at 1 year. Nivolumab, a PD1 antagonist was also approved by US FDA for third-line use that can provide durable benefit in less than 15% of patients. Other potential targets, such as Poly (ADP-ribose) polymerase (PARP) inhibition and antibody-drug conjugates targeting Delta like canonical Notch ligand 3 (DLL3), had showed some encouraging activity in early phase clinical trials. Clearly, patients need more effective therapies for advanced SCLC. The researches on promising biomarkers for specific subpopulation are also crucial to guide the treatment.

With the advance of molecular biology, researchers recently developed a new model of SCLC subtypes defined by differential expression of transcription regulators. By defining the unique therapeutic vulnerabilities of these subtypes of SCLC may accelerate therapeutic researches. It will lead targeted approaches rationally and may ultimately improve clinical outcomes for patients with SCLC.

The role of NGS in NSCLC: First-line and beyond

次世代定序在非小細胞肺癌診療的應用

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Next generation sequencing (NGS), or massive parallel sequencing, has revolutionized the approach to study cancer genetics by enabling the detection of sequence variants at unprecedented large scale. It is capable of detecting a wide variety of genomic sequence variants, such as single-nucleotide variants (SNVs), insertions and deletions (indels), copy number variations (CNVs), and structural rearrangements. NGS allows for sequencing the entire genome (whole-genome sequencing), the coding region (whole-exome sequencing), or a specific panel of genes (targeted sequencing).

In the past decades, NGS has been rapidly adopted in the clinical practice as a cost-effective and high-throughput approach. Compared with traditional methods, it can simultaneously analyze large numbers of clinically relevant genetic alterations with a single test. Among various NGS assays, targeted next-generation sequencing has the advantage of lower required amount of input material, shorter turn-around time, higher depth of coverage and greater sensitivity, and has become the method of choice for application in clinical oncology.

The clinical utility of NGS assays continues to expand. In non-small cell lung cancer, in addition to identification of therapeutic targetable alterations such as EGFR, ALK, ROS1, BRAF, MET, and NTRK, NGS is also commonly used to investigate mechanisms of acquired resistance. Recently, tumor mutational burden, which may be determined by either whole-exome sequencing or targeted sequencing, has emerged as a promising biomarker that correlates with clinical benefit from immune checkpoint inhibitors. Microsatellite instability (MSI), another predictor of a response to immune checkpoint inhibitors, can also be detected using NGS-based assays with various computational methods. Finally, plasma-based NGS assays are rapidly emerging as a useful alternative approach for molecular testing, with many promising clinical applications such as early detection of cancer, residual disease detection, response monitoring, molecular profiling, identification of resistance mechanisms, and monitoring of clonal dynamics.

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到院前緊急醫療救護對致命性急症之決定性和前瞻性角色

The Decisive and Prescient Role of EMSS in Time-Sensitivity Emergency Disease

時 間：108年6月22日 08:00~12:00

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Place：Conference Room 101C
Taipei International Convention Center

到院前緊急醫療救護對致命性急症之決定性和前瞻性角色

The Decisive and Prescient Role of EMSS in Time-Sensitivity Emergency Disease

Taipei EMS for out-of-hospital cardiac arrest: Present and future

臺北市到院前心肺功能停止患者緊急醫療救護的現況與未來

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Taipei City Fire Department (TFD) serves a community of 2,670,000 citizens and responds to approximately 1,900 cardiac arrests each year. The median response time for first responders is 4 minutes and 8 seconds. Bystander CPR frequency is 53%. Survival from all cardiac arrests in Taipei City is about 11% while Utstein survival rate is 44% last year (2018) .

It was all begun in 1999. TFD established the first Prehospital EMS team in the nation, and subsequently, it became the first EMS team to equip AEDs in the next year. At the same time, the EMS Medical Direction Committee, which also commenced in 2000, was the first of its kind in Taiwan helping to promote EMT competencies, set up protocols and update policies.

In 2011, Taipei City became the first city in Taiwan to train its citizen for Hands-Only CPR and launched the initiative “CPR Express” for communities to access CPR training. From 2012, the Quality Control task force was founded to review Audio/Video recordings and Electronic Patient Care Report (ePCR).

From 2013, Dispatcher-Assisted CPR program has been started. In 2014, TFD worked with Academia Sinica to make a customized bus, Heart Bus, which equipped gamification CPR coaching devices based on Kinect technologies. The bus has circulated communities and campuses since then to motivate bystander CPR.

In 2016, the country’s first EMS academy was opened in Taipei City. Focusing on high fidelity simulation, it revealed the willingness and ability of TFD’s on the EMT education. Furthermore, to mitigate the unique life-style-related restriction, all ambulances were equipped with mechanical CPR devices in 2018 for that most of our citizens are living in high-rise buildings.

TFD also prepared HP-CPR course for all crew members, and all 1,142 EMT-2 and 102 EMT-P completed the training after September 2018. Last, TFD also launched the first crowd-sourcing app in Taiwan- “Taiwan Oh My Guard” in December 2018.

To increase early CPR and AED used in cardiac arrest, pre-specified public safety response for cardiac arrest should be the next step and strive for excellence together.

Post-cardiac arrest care for OHCA patients: Where we stand and where we head for

到院前心肺功能停止病人在到院後的復甦照護：現況與展望

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Post–cardiac arrest care is a critical component of the chain of survival and the capstone of advanced life support. The epidemiology of adult out-of-hospital cardiac arrest (OHCA) incidence is about 100-112 per 100,000 person-years among developed countries, with the emergency medical services (EMS) treated percentage about 50-60%, approximately the figures that has been sent to hospitals by ambulances. These numbers didn't change much since the year 2000, but the return of spontaneous circulation (ROSC) percentage and survival to discharge rate has shown some improvements.

Besides of the medical progress in the recent two decades, several advances have played a key role in these changes. The efforts from community and EMS on enhancing prehospital CPR and resuscitation are pivotal, but the hospital care for patients with ROSC after cardiac arrest determines the final outcome, particularly the neurological performances. The precipitating causes and etiologies of cardiac arrest may vary, hence searching for the correct underlying pathology at the hospital end is fundamental to the treatment. Conventional ICU monitoring and intervention remains important with protocolized hemodynamic optimization and multidisciplinary early goal-directed therapies, such as identification and avoidance of hypotension with proper vasoactive drugs. Emergent coronary angiography is often required during the first 24 hours after cardiac arrest especially when cardiac etiology is suspected. Though routine out-of-hospital cooling after ROSC is not recommended, targeted temperature management (TTM) has been proven to have better neurologic outcome in not only ventricular fibrillation cardiac arrests, but beneficial for all comatose adult patients. After induced hypothermia achieved and maintained constantly for at least 24 hours, continuing temperature management by preventing fever post-rewarming is also suggested.

Due to the heterogeneity of post-cardiac arrest patients, in terms of the age, comorbidities, and the hypoxemia-ischemia duration, the ideal care should be tailor-made to different individuals according to their diseases and dysfunction. The state-of-art care for post-cardiac arrest patients has not been completely defined, and there is still a huge gap to be filled with more researches and investigations.

The mission and role of emergency medical service in acute myocardial infarction

緊急醫療救護在急性心肌梗塞的角色與任務

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Emergency medical service (EMS) means the medical practice in the prehospital environment. It helps the patient who is in critical condition. Emergency medical Technicians (EMTs) are the personnel who received professional medical training and performing medical care in out-hospital flied. An excellent EMS system can work efficiency and decreases the mortality of serious illness.

Acute myocardial infarction (AMI) is a time-sensitivity emergency disease. The mortality and morbidity of AMI is highly related to the onset-to-reperfusion time. Patient who had AMI attack may call for Ambulance help to sent to hospital at the beginning. Thus the management on the scene and ambulance can affect the prognosis of patient.

The typical presentations of AMI include chest tightness, radiation pain, cold sweating and dyspnea, etc. EMT needs to identify the patients who may have AMI according to these symptoms and signs and provide appropriate management in these high risk groups. Base on the AHA guideline, administer Aspirin and consider oxygen, NTG and morphine were suggested in EMS system. If they could obtain 12-lead EKG and notify the receiving hospital that the patient with AMI, Door-to-needle time can be shorten significantly. The Prehopsital notification about AMI is also can decrease the mortality and morbidity.

Taipei City is the capital city of Taiwan and has about 2.6 million populations. How to build an efficiency 12-lead EKG transmitting system is import to the citizen. In this speech, we will share the experience and future vision about the progression of AMI care in EMS. Hope can improve the medical care in the out-hospital environment.

The ED management of patient with suspected acute coronary syndrome after dispatched

疑冠心症病患到院後處置

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Acute coronary syndrome (ACS) is a medical emergency that put a considerable challenge to primary healthcare providers. It consists ST-elevation Myocardial infarction (STEMI) and Non-ST elevation ACS. STEMI is diagnosed based on Electrocardiographic (ECG) change made within 10 minutes after ED presentation. The diagnosis of Non-ST elevation ACS, however, is often required a combination of ECG change, clinical judgment and an elevation of cardiac biomarker. All patients with suspected ACS should be early recognized and early reperfusion management if required.

In recent studies, the numbers of Non-ST elevation ACS have increased gradually. The primary healthcare providers might be faced the difficulty in diagnosis, management and treatment. Therefore, Taiwan Society of Cardiology had published an updated guideline for management for Non-ST elevation ACS, which based on the recent evidence and recommendations. This include the utility and clinical application of high sensitivity troponin assay. The newer biomarker could provide more than 99% of negative predicative rate for acute MI. As to the pharmacologic antithrombotic therapy, aspirin combination with either Clopidogrel, Ticagrelor, Prasugrel or other Glycoprotein IIb/IIIa receptor antagonists is considered. Meanwhile, all patients with suspected high-risk ACS should receive early reperfusion therapy promptly.

Taipei Veteran General hospital is a tertiary medical center with about more than eighty-thousands ED visits annually. In this review, we would like to show the recent update evidence of management in ACS patients. Meanwhile, we would also like to share our experience in the recognition, initial management, and pharmacologic therapies to the patients with acute coronary syndrome in ED.

The prehospital strategy in the era of endovascular thrombectomy for stroke patients

對於中風取栓時代下的院前因應策略

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Endovascular thrombectomy (EVT) has been shown to be beneficial to selective patients with large vessel occlusion (LVO). It has also been shown that, like intravenous thrombolysis with recombinant tissue plasminogen activator, the shorter the time interval between the onset of symptoms and reperfusion using EVT, the better the functional outcome at three months. Therefore, it is suggested that emergency medical service (EMS) systems should adopt the use of a field stroke severity scale to identify patients with suspected LVO, and that the patients be classified accordingly. State-wide and county-wide protocols for EMS systems that include a bypass strategy for patients with suspected LVO have been implemented in the United States.

However, although a bypass strategy for LVO benefits patients receiving endovascular thrombectomy, it may delay some patients from receiving intravenous thrombolysis. Therefore, many prehospital strategies for transporting patients suspected of stroke have been suggested to solve the problem. Some EMS systems chose high-sensitive prehospital stroke scales to identify patients with LVO, while the others did not. The reason why they had different choices might be that their EMS systems and the locations of hospitals were quite different among them.

The stakeholders in the EMS systems in Taiwan should try to choose and even design a suitable prehospital strategy to provide the best care for stroke patients.

Acute infarction algorithm, pre-interventional assessment and endovascular treatment: Taipei Veterans General Hospital experience

急性中風到院後評估流程及取栓治療：臺北榮總經驗

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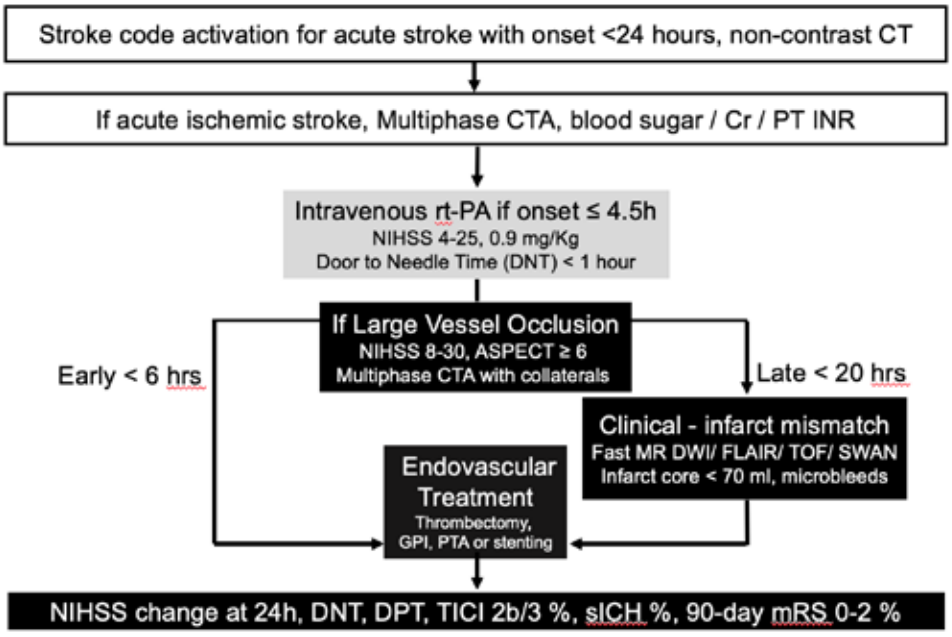
1. Acute infarction algorithm:

Suspected acute infarction patient arrived ER onset within 20 hours, The triage staffs will activate green express channel. Neurology department duty physician will received text message simultaneously. Patient was sent to emergency room immediately and obtained ECG, blood routine and biochemistry. Patient will send to emergent brain CT room for brain CT and multiphase CTA.

2. Pre-interventional assessment

Neurologist will complete assessment within 45 minutes including onset time, NIHSS, brain imaging (large artery occlusion, ASPECTS, collateral status) and lab data. Patient who eligible for IV thromblysis will received alteplase at emergency room. If onset within 6 hours, We will start endovascular treatment in large vessel occlusion stroke patients. Otherwise, we will arrange fast-MR including FLAIR, DWI, ToF and SWAN to confirmed infarct core. We will arrange endovascular thrombectomy with infarct core size less than 70 mL.



3. Endovascular treatment

In TVGH, our endovascular procedural is under general anesthesia. Patient received endovascular treatment after complete anesthesiologist evaluation. We did not use balloon guiding catheter due to NHI guideline. We used shuttle or long sheath as guiding catheter with penumbra system 060 or Sofia 070 as intermediate catheter. The microwire and microcatheter were in various as current simulation and interventionist discretions.

Out of hospital care for major trauma: Now and the future

重大創傷到院前照護的現況與進展

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Major trauma is the first leading cause of death in young generation. Thousands of youth are killed or disable after the major trauma accident every year in Taiwan. And this cause a big burden on society and the family economy. The best way to decrease the mortality is to prevent the accident happening. After the catastrophic events were happened, excellent out of hospital care played an important role to reduce the damage.

Base on the previous studies, we already knew that the prognosis of major trauma was highly related with the time between accident-onset and operation. Thus on-scene time less than ten minutes and onset to operation less than one hours were the golden guideline in the major trauma management. The only three managements that could help the injury are protect airway, protect C-spine and control bleeding. Otherwise, no other treatment was proved to be benefit in these groups in out of hospital field. Sending the injury to level 1 trauma center directly also can reduce the mortality and morbidity according to the published study in NEJM 2006. Therefore, the government need to identify the resuscitation ability of regional hospitals and set the bypass policy for the prehospital care. Then the implement with Out-of-hospital activated trauma team shorten the waiting to the operation room. Finally, an excellent trauma registry is also an necessity to the trauma care system in order to follow-up the outcome

Currently, there are some new scientific evidences that may improve the outcome of major trauma. High dosage Transamine using, fluid resuscitation protocol and massive transfusion protocol etc may help the injury. Taipei City has the best emergency medical service system in Taiwan and serves about 2.6 million populations. Trauma accounts for about 40% in the all emergency calls. In this speech, we will review the latest vision about the prehospital care major trauma.

Six publications you must know in managing major trauma patients

六篇你必須知道的創傷照護治療文獻

Meng-Hsuan Chung

鍾孟軒

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臺北榮民總醫院 外傷醫學科

The rapid advancement of trauma care is often, sadly, firmly linked to warfare. The crisis of injury created by war has often led to innovation in trauma care and surgical creativity, and many of our best practices were forced by war into widespread adoption. Others simply evolved into practice through a natural pathway of peer review, publication, and acceptance by the trauma community.

Research on the management of severe injury is extremely challenging to conduct, and innovation is often driven by necessity rather than by the scientific method. Nevertheless, survival rates after severe injury are higher now than at any point in recorded history, and recent improvements in care are attributable, in part, to the nearly two decades of war on terrorism.

In this review, we choose six journal articles published in related to trauma and acute care surgery from 2016~2019, which was important and emphasized on major advances in the care of severely injured patients. Some interventions are mechanical, some are pharmacologic, and others are philosophical and require a new way of thinking. By discussing in this session, it may benefit our society for better care and management of critically-injured patients in trauma.

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多專科團隊應用於治療局部侵犯型直腸癌和第四期直腸癌

Applications of Multidisciplinary Team to Treat Locally Advanced Rectal Cancer and Stage IV Rectal Cancer

主辦單位：中華醫學會
協辦單位：臺北榮民總醫院60週年院慶
中華民國大腸直腸外科醫學會
社團法人中華民國大腸直腸癌關懷協會

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Place：Conference Room 101A
Taipei International Convention Center

多專科團隊應用於治療局部侵犯型直腸癌和第四期直腸癌

Applications of Multidisciplinary Team to Treat Locally Advanced Rectal Cancer and Stage IV Rectal Cancer

The changing and unchanged roles of radiotherapy in advanced rectal cancer

放射治療在侵入型直腸癌治療角色的演進

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Radiotherapy is the integrative part of multimodality treatment of locally advanced rectal cancer. The role of radiotherapy (RT) as an adjuvant or neo-adjuvant treatment to surgery in locally advanced rectal cancer has been established as it reduces local recurrence, improved survival and/or increasing the chance of organ preservation. However, there are still many issues need to be addressed: such as should radiotherapy be administered before or after surgery? short course radiotherapy vs long course chemo-radiotherapy; optimal Interval between radiotherapy and surgery in the preoperative approach; a rising paradigm of total neo-adjuvant chemotherapy (TNT) and selective elimination of radiotherapy or surgery after TNT treatment. In this presentation, the above issues will be discussed and the experiences from our hospital will also be presented.

Liver resection for patients with colorectal cancer liver metastases: Single center experience

大腸直腸癌肝轉移病人之肝臟切除：單一醫院經驗

Te-Hong Chen

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Background: We report our experience with liver resection for patients with Colorectal liver metastases in China Medical University Hospital.

Methods: Retrospectively analysis of prospective collective clinical data of 224 patients with colorectal liver metastases, received curative liver resections from 2003 to 2016.

Results: During the period of 2003 to 2016, a total of 224 patients underwent curative liver resections. Among these patients, 133 (59.4%) had synchronous colorectal cancer and liver metastases. Of the 133 patients with synchronous tumors, 63 (47.4%) had simultaneous resection of the colorectal tumor and the liver tumor. Twenty-five patients (11.2%) had extra-hepatic metastases. One hundred one(45.1%) patients had more than one metastatic tumor, and the mean tumor size was 30.1±21.8 mm. The tumor location include all segments. Eighty-eight(39.3%) patients received major hepatectomy and 112 (50.0%) patients underwent liver resection laparoscopically. The mean operation time was 307.5±148.6 minutes, mean blood loss was 384.7±441.6ml, and 33(14.7%) patients need blood transfusion. The mean resection margin was 6.6±7.3 mm. Margin positive rate was about 8.5%. The mean hospital stay was about 8.5±4.7 days. There were 2 mortalities, and morbidity rate was 18.8 %. The median follow time was 33.3 months. Disease-free survival at 1, 3, and 5 years was 50.1%, 27.5%, and 19.5%, respectively. Overall survival at 1, 3, and 5 years was 94.5%, 65.6%, and 53.6%, respectively.

Conclusion: Liver resection for colorectal cancer liver metastases can provide a satisfactory oncologic outcome in selected patients.

Lateral pelvic lymph node dissection in locally advanced rectal cancer

骨盆腔側壁淋巴結廓清術治療局部侵犯性直腸癌

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In western countries, lateral nodal disease has been generally considered as distant metastasis. While in Japan, lateral nodal disease has been treated as regional disease. According to Japanese studies, T3/4 rectal cancers that extend below the peritoneal reflection have 15-20% incidence of lateral pelvic lymph node metastasis. Lateral pelvic lymph node dissection without chemoradiotherapy achieved 40-50% 5-year overall survival in patients with lateral node metastasis, suggesting that lateral node metastasis is oncologically identical to mesorectal N2 disease. A recent randomized trial that compared TME alone vs. TME with lateral pelvic node dissection for patients with T3-4 low rectal cancer without enlarged lateral nodes, demonstrated decreased local recurrence in the lateral pelvic node dissection arm. These evidences strongly indicate that lateral node metastasis is regional and can be cured by surgical dissection.

In western countries, it has been assumed that lateral local recurrence can be prevented by neoadjuvant therapy. However, recent studies demonstrated high local recurrence after neoadjuvant chemoradiotherapy and TME without lateral pelvic node dissection in patients with enlarged lateral pelvic nodes. Chemoradiotherapy alone may decrease, but never eliminate lateral node metastasis. A recent retrospective study from Japan that combined neoadjuvant chemoradiotherapy and selective lateral pelvic lymph node dissection reported excellent outcomes with 2.7% local recurrence and 84% relapse free survival at 3 years in patients with clinically enlarged lateral nodes. These data supports the hypothesis that lateral nodal disease may be regional and can be cured by combining surgical resection with chemoradiotherapy.

Surgical treatment of lung metastasis with colorectal origin

大腸直腸癌肺轉移的手術治療

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With the introduction of multi-modality treatment, the survival of lung metastasis of colorectal cancer has been improved with time. For these patients, surgery can provide a definitive treatment and in conjunction with other treatment modality, provide a best chance of long-term survival. From the experience of surgical treatment for such patients with VATS (video-assisted thoracic surgery), the 5-year survival is 48%. The number of metastasis is a significant prognostic factor with the best survival outcome for the patients with single metastatic lesion with 64% of 5-year survival rate. For these patients, minimally invasive surgery with single or reduced port VATS and technique of tumor localization has been evolving an effective treatment option for a definitive and yet minimally invasive treatment route.

Preoperative treatment for locally advanced rectal cancer

局部侵犯性直腸癌術前治療

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The introduction of total mesorectal excision (TME) and preoperative radiotherapy (RT) were treatment revolutions that resulted in improved local control after curative resection for rectal cancer. However, local relapses still occur, even in the era of TME, and remain a cause of recurrence worldwide. The high rate of distant metastasis after curative resection remains a problem. Furthermore, the introduction of newly developed cytotoxic agents into the LARC treatment strategy continues to be an ongoing challenge. Shifting part of an adjuvant chemotherapy (CTx) regimen to the preoperative period is a promising strategy. Currently, various novel methods, such as induction CTx, consolidation CTx, concomitant administration with RT, and neoadjuvant CTx without RT, have been attempted worldwide. Although some strategies have shown favorable short-term outcomes, the long-term efficacy of the treatments needs be evaluated. At the same time, we must investigate clinical and/or molecular biomarkers to predict the therapeutic effects of each treatment, which is the fastest route to providing ideal personalized therapy for patients with LARC.

Planned short-course radiation is superior to upfront CCRT in treating metastatic rectal cancer

轉移性直腸癌短療程放射治療比長療程的化療合併放療佳

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Background: To compare the cost-performance between planned short-course radiation and upfront concurrent chemoradiation on metastatic rectal cancer.

Methods: A total of 75 patients with metastatic rectal cancer who underwent planned short-course radiation or upfront concurrent chemoradiation were enrolled. The Kaplan-Meier method was used to compute the survival rates. The χ^2 test was used to compare baseline characteristics. The Cox proportional hazards model was applied to determine the prognostic influence of clinicopathological factors.

Results: The planned short-course radiation is superior to upfront concurrent chemoradiation in overall survival for the patients with metastatic rectal cancer (34.8 vs. 20.2 months, P=0.010). The planned short-course radiation was an independent prognostic factor (P=0.009, HR (95% CI) = 0.319(0.135-0.752)). The efficacy of radiation on down-staging was similar between planned short-course radiation and upfront concurrent chemoradiation. The total cost of concurrent chemoradiation is 4.52-fold more expensive than short-course radiation (340,142 vs. 75,106 NT dollars, respectively).

Conclusion: Based on the impressive cost-performance of planned short-course radiation compared with upfront concurrent chemoradiation (better OS, modest down-staging and lower cost), planned short-course radiation should be the preferred radiation approach for managing metastatic rectal cancer.

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泌尿內視鏡手術在非腫瘤手術之現況

Contemporary Development of Non-oncologic Endourological Surgeries

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Place：Conference Room 101D
Taipei International Convention Center

泌尿內視鏡手術在非腫瘤手術之現況

Contemporary Development of Non-oncologic Endourological Surgeries

Development of laparoscopic/robotic surgery for urinary incontinence

腹腔鏡 / 機器手臂尿失禁手術之發展

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Stress urinary incontinence (SUI) is a prevalent condition affecting 25% to 35% of the US women. The current lifetime risk of surgery for SUI in the United States is approximately 13.5% with an estimated 200,000 female undergoing surgical repair annually. These rates are predicted to increase in the coming years due to an aging population. SUI is generally attributable to urethral hypermobility as a result of diminished urethral support, although there can also be a component of urethral sphincter weakness.

In women with incontinence secondary to urethral hypermobility, pelvic floor muscle training is the first-line treatment for SUI, and if this fails, colposuspension surgery is a traditional repair that surgically elevates and reinforces periurethral tissue. Although once considered the “gold standard” in SUI treatment, the number of colposuspension procedures has limited since the turn of the twenty-first century following the introduction of the midurethral sling.

Actually, over the past twenty years, minimally invasive urethral sling procedures have become the main operations of SUI treatment nearly 90% of all surgeries in the United States in 2009. However, the Food and Drug Administration notification on serious complications associated with transvaginal mesh in 2011, the negative publicity associated with vaginal synthetic mesh products has extended to urethral slings. Subsequently, the interest in colposuspension procedures has been relighted as both women and practitioners alike seek alternative SUI treatment options. As a result, the Burch procedure continues to have a place in the operative opinions of the urologist and gynecologist. Iterations of the procedure, including mini-incisional approaches, laparoscopic, and robotic, appear to have equal efficacy to the open procedure with minimal complications. Robotic Burch colposuspension can be completed in a safe and effective manner and should be considered as an option for patients in whom an anti-incontinence procedure is indicated and who are already undergoing robotic surgery.

Development of laparoscopic/robotic reconstruction for upper urinary tract

腹腔鏡 / 機器手臂上泌尿道重建手術之發展

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Laparoscopic urological surgery was first reported in 1991. The advancement in optic technology, instrument design and application of advanced electrocauterization has made enormous improvement in laparoscopic reconstruction for upper urinary tract. Currently, laparoscopic reconstruction of upper urinary tract has become the treatment of choice for patients with complex urological conditions.

Robotic techniques have been increasingly adopted by urologists for reconstruction of the upper urinary tract since early 2000s. The improved dexterity, visualization, and ergonomics of robotic systems have applied naturally to reconstruction and have facilitated intracorporeal suturing compared with traditional laparoscopy. In particular, robotic techniques have been used for anastamotic suturing during minimally invasive pyeloplasty.

This review will focus on the development of laparoscopic/robotic surgery for the reconstruction of upper urinary tract. The surgical approach, operative time, perioperative morbidity, hospital stay and postoperative morbidity will be discussed., The long term outcome comparing conventional, laparoscopic and robotic reconstruction of upper urinary tract will be reviewed. The newly advancement in this urological field will be described in details so as to provide a panoramic understanding of laparoscopic/ robotic reconstruction of upper urinary tract.

Development of laparoscopic/robotic surgery of urolithiasis

腹腔鏡 / 機器手臂尿路結石手術之發展

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The best modality for treatment of large proximal ureteral stone is still in debate. We conducted a retrospective study to compare the hospital stay, operative time, stone clearance rate, complication and cost between laparoscopic and robotic ureterolithotomy instead of traditional ureteroscopic lithotripsy from single team experience. And we also reported a case series study of an alternative method to manage large renal stone with robotic assisted laparoscopic technique.

Overview of technical aspects of RIRS

逆行性腎內手術的技術綜觀

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1. Anesthesia

Although spinal anesthesia is an available option, general anesthesia is suggested for RIRS for two reasons. First, due to larger tidal volume, breathing movement can disturb the surgeon during navigation and lithotripsy. In addition, mechanical ventilation can be stopped temporarily as needed. Second, for larger stones, the time frame for spinal anesthesia can be exceeded, requiring a second general anesthesia to finish the procedure.

2. Access to the ureter and placement of ureteral access sheath

Although the procedure usually starts with cystoscopy to place a guidewire into the kidney, the procedure may start directly with a first-look semirigid ureteroscopy. The advantage of doing this is that the whole ureter is passively dilated under direct vision while exactly assessing the compliance of the ureter to identify the ideal ureteral access sheath (UAS) size, according to the patient's anatomy. Moreover, the presence of ureteral stricture can be easily detected before the placement of UAS. Furthermore, missed fragments that migrated down into the ureter can be removed before UAS placement.

For the placement of UAS, use of superstiff guidewire may help easier advancement of UAS. The ideal position of the UAS is with its distal extremity just below the ureteric–pelvic junction (UPJ). In fact, its advancement into the kidney may damage the UPJ and the flexible ureteroscope when navigating in full deflection.

3. Lithotripsy

It is advisable to keep the laser fiber tip at a minimal distance from the stone (1–2 mm) and to move it as if painting on the stone's surface in an effort to prevent perforation of the stone with consequent formation of big fragments that might become difficult and time consuming to treat. For hard stones, other strategies can be used, such as chipping or fragmenting, and "popcorning" is considered useful to finalize lithotripsy of multiple small fragments into smaller debris.

Development of benign prostatic hyperplasia surgeries

良性攝護腺肥大手術的進展

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Taiwan has entered the aging society for years. And we would be aged society on 2018. The prevalence of lower urinary tract symptoms (LUTS) is getting higher and higher with this aging process globally. Urologists confront more and more challenges with benign prostatic obstruction (BPO) . We are having more medical choices for BPO with less side effects than before. However, medical treatment has its limitation, we still need the surgical intervention for the BPO.

We have only open prostatectomy for the BPO in the early 1970s. The veteran hospital had sent their young urologist to USA for the TURP. Then TURP fluorished in the coming 20-30years. Greenlight laser appeared at the end of 2004. And it bloomed as a brand new treatment modality for its safety profile and compatible clinical result. Then, around 2006, thulium laser launched in Taiwan for its high efficiency and availability of prostate tissue for pathological examination. Thulium laser was applied as vapo-resection first, and around 2010, some urologists tried to perform prostate enucleation with thulium laser. Now , prostate enucleation has more and more popular in Taiwan.

Holmium-YAG laser has become the most popular laser applied in prostate enucleation as HOLEP globally. However, most of the enucleation urologists perform with thulium laser in Taiwan. It might be owing to the lack of high power holmium laser in the early years. After all, prostate enucleation is the standard operative procedure for the BPO. With this surgical technique, we could step closer to the treatment of LUTS.

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頑固的青光眼：跨專科對談

Complicated Glaucoma : A Multi-subspecialty Discussion

主辦單位：臺北榮民總醫院眼科部
協辦單位：中華民國眼科醫學會

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Place : Conference Room 103
Taipei International Convention Center

頑固的青光眼：跨專科對談
Complicated Glaucoma : A Multi-subspecialty Discussion

Secondary glaucoma in corneal diseases

角膜疾病和續發性青光眼

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Two corneal endothelial disorders are highly associated with the development of secondary glaucoma. One is iridocorneal endothelial (ICE) syndrome, the other is posterior polymorphous dystrophy (PPMD). The corneal endothelial cells may migrate over the trabecular meshwork onto the iris, bringing along a membrane that impairs aqueous humor outflow. Resultant elevations in intraocular pressure (IOP) may become difficult to control, making the management of glaucoma associated with these disorders challenging. Glaucoma filtering surgery is often required to control elevated IOP in ICE syndrome, but less often in PPMD. Trabeculectomy with mitomycin C may be effective initially, but eyes with ICE syndrome are prone to bleb failure, as the endothelial membrane migrates over the sclerostomy. Nd:YAG laser goniopuncture of the membrane can restore flow through the sclerostomy, but the effect is usually short-lived as the membrane recovers. The tube of tube-shunt surgery should be kept long and inserted away from the cornea and the iris' surface to lessen the risk of blockage by the proliferating membrane. Sulcus or pars plana placement of the tube may decrease the likelihood of its occlusion and lessen the potential damage to the already compromised cornea or graft.

Secondary glaucoma after corneal surgery is common. Glaucoma may be due to multiple mechanisms such as peripheral anterior synechiae formation, trabecular meshwork dysfunction from inflammation and steroid-induced ocular hypertension. Uncontrolled glaucoma adversely affects graft survival in turn. The relatively high rate of glaucoma development or worsening after penetrating keratoplasty (PKP) has significant implications leading to corneal graft failure and irreversible vision loss from glaucomatous optic neuropathy. In contrast, Descemet's stripping with automated endothelial keratoplasty (DSAEK) may provide advantages over PKP with lower risk of serious, vision-threatening glaucoma-related complications.

Diagnosis and management for uveitic glaucoma

葡萄膜炎次發青光眼的診斷和治療

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Secondary glaucoma due to uveitis, or uveitic glaucoma, is sometimes difficult to treat because of the large fluctuations in intraocular pressure (IOP) and the complicated causes for IOP elevation. To consider the mechanism of rising IOP, observation of angle and inflammatory cells in the anterior chamber, and the information about the timing of corticosteroid use and IOP elevation is essential. If there are few angle adhesions and less inflammation in the anterior chamber, the possibility of steroid-induced glaucoma should be considered. In uveitic glaucoma, the fluctuations of IOPs become sometimes large, leading to the visual field deterioration. Thus, it is necessary to be careful of the visual field change even if the IOP seems to be well-controlled.

As for drug selection in uveitic glaucoma, it is generally considered that an aqueous production inhibitor (β-blocker, carbonic anhydrase inhibitor) is more effective than an aqueous outflow promoter (prostaglandin analogues (PGs), α-adrenergic agonists). Some reports demonstrated that topical pilocarpine and PGs may cause deterioration of iritis and cystoid macular edema (CME) in cases with uveitis, but some reports demonstrated that PGs had not increased the incidence of iritis and CME. Rho-associated protein kinase (ROCK) inhibitors are expected to be effective in steroid glaucoma because they inhibit extracellular matrix deposition on the trabecular meshwork by steroids.

If medications do not result in IOP decrease, application of glaucoma surgery should be considered. Trabeculectomy and trabeculotomy (including ab interno) are mainly performed, and the selection of operative procedures will be considered from the condition of the angle, target IOP, and the condition of the remaining visual field. The control of intraocular inflammation during pre- and post-operative periods is important, especially in trabeculectomy, because the recurrence of iritis within 3 months after trabeculectomy sometimes leads to disappearance of filtering bleb, which may worsen IOP control.

In the presenting talk, I will introduce useful knowledge for treatment in uveitic glaucoma.

Biography

1992 Resident in Ophthalmology, The University of Tokyo School of Medicine

1993 Clinical fellow in Ophthalmology, Musashino Red Cross Hospital

2001 Ph.D., Graduate school of Medicine, The University of Tokyo School of Medicine

2001 Research associate in Ophthalmology, The University of Tokyo School of Medicine

2007 Assistant Professor in Ophthalmology, The University of Tokyo Graduate School of Medicine

2016 Associate Professor in Ophthalmology, The University of Tokyo Graduate School of Medicine

Treatment of uveitis and its impact on IOP

葡萄膜炎的治療和其對眼壓的影響

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Uveitis is a sight-threatening disease with more than 60 etiologies. 70% of uveitis patients might have suffered from decrease of vision temporally or permanently. Ocular complications related to intraocular inflammations are main causes of visual impairment in these patients. Studies have shown that 7% to 20% uveitis patients would experience ocular hypertension or glaucoma. Patients with uveitis would develop ocular hypertension and glaucoma through several processes. The inflammation might change the permeability or obstruct the outflow of aqueous in the anterior chamber angles and lead to an increase of intraocular pressure. Excepting inflammation itself, corticosteroid, the mainstay of uveitis treatment, might also cause the elevation of the intraocular pressure through several mechanisms. The elevation of intraocular pressure might be mild or transient at first. However, the persistence or recurrence of ocular hypertension may damage the optic nerve and results in ganglion cells apoptosis.

Systemic treatment for uveitis was usually required if intraocular inflammation threatens a patient's vision or cannot be controlled locally and when it is associated with systemic diseases. Corticosteroids and immunomodulatory chemotherapy are the conventional initial treatments. However, the various side effects of these therapies increase the burden on patients, not only physically but also mentally. Moreover, uncontrolled inflammation and poor visual outcomes have sometimes been recorded despite the combination of these medications or their high dosage.

In the presenting talk, I will introduce the most recently treatment for uveitis, and discuss about its impact on patients' intraocular pressures.

Secondary glaucoma related to retinal diseases

視網膜疾病與續發性青光眼

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Various types of glaucoma are either caused by or are associated with retinal diseases. These retinal disorders include retinal detachment, retinitis pigmentosa, retinal venous occlusion and retinal arterial occlusion. In addition, the treatment of retinal disorders can lead to an open- or closed-angle glaucoma. Open-angle glaucoma may be caused by intravitreal injection of steroid or silicon oil. Closed-angle glaucoma may be due to scleral buckle, intravitreal gas, silicon oil or laser photocoagulation. This section will describe and discuss the major variants of glaucoma associated with retinal diseases.

High intraocular pressure after cataract surgery

白內障患者術後高眼壓的鑑別與處理

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張毓帆

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Cataract surgery is the most common surgery performed by ophthalmologists. Most patients gain satisfactory outcomes, while surgeons sometimes encountered post-operative complications. What's more important is the post-op related complications or situations that need to be taken care of. Intraocular pressure (IOP) may rise even after uncomplicated cataract surgery, which further intervention may be needed. The IOP elevation is usually immediate and transient around 5-7 hours after surgery. The reasons for IOP spike includes retained ophthalmic viscoelastic materials, intraocular inflammation, hyphema, peripheral anterior synechia, or damage to trabecular meshwork. Although some of these effects may be blunted under topical IOP lowering medication used in advanced, it remains significant in many patients.

There are several risk factors that may increase the post-op IOP elevation, such as residual viscoelastic materials, patients with history of glaucoma, surgeons experience, axial lengths, post-op corticosteroid use with cases of steroid responder, and severe post-op inflammation related pupillary block. To carefully detect the cause of IOP spikes and manage it in the correct way is also important. For those with intractable IOP control, further surgical or laser intervention are essential options. Finally, do keep in mind for those sight-threatening complications related to IOP elevation such as retinal vascular occlusion, progressive field loss in advanced glaucoma, and anterior ischemic optic neuropathy in susceptible patients.

Minimally invasive glaucoma surgery (MIGS)

微創青光眼手術

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Current management of glaucoma is suboptimal. Some treated patients still go blind due to late presentation, insufficient IOP reduction or poor compliance. Filtering surgery can achieve a more constant and lower IOP than medication and therefore should be performed in patients with progressive disease despite maximal tolerable medication. However, filtering surgery is frequently delayed and treated as the last resort in glaucoma management because of the potential complications.

XEN gel, a microinvasive glaucoma surgery (MIGS) device, is designed to lower IOP through subconjunctival flow with an attempt to eliminate postoperative hypotony and early postoperative discomfort associated with trabeculectomy. XEN gel implantation can achieve comparable IOP control as trabeculectomy with similar safety profile although XEN gel may need more postoperative intervention such as needling. However, XEN gel implantation is associated with less tissue destruction and more rapid vision recovery comparing to trabeculectomy. These benefits may make XEN gel implantation being implemented earlier in disease course to obtain lower and less variable IOP, ideally addressing the inadequacy of current glaucoma management - the under-treatment and noncompliance issues.

In this presentation, I will share the preliminary experience with XEN gel implantation in our hospital.

Corneal diseases secondary to glaucoma treatment

青光眼治療併發之角膜病變

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Glaucoma treatment may induce cornea and ocular surface pathologies. The effects can be categorized into 1) toxicity of the therapeutic agents, 2) endothelial damage, and 3) effects on visual quality.

Surface toxicity due to preservatives in the pressure lowering agents has long been stressed. Other side effects include inducing neurotrophic, allergic, and inflammatory reactions. The most toxic agent is mitomycin C due to its non-selective inhibition of proliferation of all kinds of cells.

Severe corneal endothelial damage end up with decompensation is not rare in patients undergone multiple surgery for glaucoma treatment. Argon laser peripheral iridectomy used to be the number one indication for corneal transplantation in Japan. Corneal transplantations in these patients bear higher risk. Poor pressure control usually leads to graft failure.

Central visual quality is greatly affected by pupil size and location especially in patients post penetrating keratoplasty. Increase of ocular high order aberrations are observed after trabeculectomy.

In this speech I will present cases to demonstrate various pathologies secondary to glaucoma treatment.

Ptosis following trabeculectomy

青光眼術後的眼瞼下垂

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Postoperative ptosis can occur following various ocular surgery especially after glaucoma surgery which can lead to cosmetic and functional defects. It can occur through multiple mechanisms including lid edema from locally administered anesthetic, initial myotoxic effects, and the compression of the upper eyelid against the orbital bones from the eyelid speculum. To identify potential risk factors and adjust the operative techniques can decrease the rate of postoperative ptosis. Management of postoperative ptosis following glaucoma surgery will also be adjusted according to the location of the bleb and shunting devices.

臺北榮民總醫院60週年院慶
暨中華醫學會108年度聯合學術研討會

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頭頸癌器官保留治療的最新進展

Recent Advances of Organ Preservation Therapy in Head and Neck Cancer

時 間：108年6月22日 13:30~17:10
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臺北榮民總醫院60週年院慶暨中華醫學會108年度聯合學術研討會

頭頸癌器官保留治療的最新進展

Recent Advances of Organ Preservation Therapy in Head and Neck Cancer

Changing trend of therapeutic modalities of oropharyngeal cancer in VGH-TPE

臺北榮總口咽癌的治療趨勢

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Oropharyngeal cancer in particular has been on the rise, and it is expected to constitute the majority of all head and neck cancers. Over the past decades, there has been a paradigm shift toward organ preservation therapy because surgical excision for advanced tonsillar squamous cell carcinoma is technically demanding and frequently associated with post-treatment cosmetic and functional sequelae. The combination of chemotherapy with radiotherapy in organ preservation treatment has been demonstrated to offer comparable treatment outcomes to primary radical surgery with adjuvant RT/CRT for advanced oropharyngeal SCC. However, high rates of acute high toxicities along with late treatment sequelae can be observed under intense CRT treatment. Advances in treatment over the past years have led to more widespread use of minimally invasive surgical procedures in the selective patient population with oropharyngeal cancer. The alternative offers the ability to tailor therapy and may provide superior functional outcomes even when adjuvant therapy is indicated.

On the other hand, the incidence of patients diagnosed with HPV-related oropharyngeal SCC is increasing in the western countries. Nevertheless, this group has a better prognosis than their HPV-negative counterparts but several studies have suggested that among HPV-positive patients those with a smoking history had worse oncological outcomes. Epidemiologic studies have shown a wide variation of incidence between worldwide areas. These prevalence and oncologic outcomes in the betel quid chewing area are not often studied.

In this presentation, we'd like to share the trend of therapeutic modalities, epidemiology and treatment outcomes associated with HPV and consumption of alcohol/betel quid/cigarette of oropharyngeal SCC in Taipei Veterans General Hospital from 2011 to 2017. In addition, we characterize the tumor staging changes from the AJCC 7th to 8th editions and appraise the prognostic impact of the new AJCC-8ed staging system relative to the previous AJCC-7ed system.

The treatment paradigm and outcome of oropharyngeal squamous cell carcinoma in National Taiwan University Hospital

口咽癌治療趨勢與台大醫院口咽癌存活分析

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In developed Western countries, HPV+ oropharyngeal squamous cell carcinoma (OPSCC) is more common than HPV− OPSCC nowadays. For example, in the United States, HPV+ OPSCC accounts for more than 70% of all OPSCC. It is well known that HPV+ OPSCC is a totally different disease than HPV- OPSCC. Comparing to the HPV- OPSCC, it is well known that HPV+ OPSCC had significant better disease control and survival outcomes. Therefore, there are many clinical trials which targeting the treatment de-escalation for HPV+ OPSCC are ongoing in western countries. However, in Taiwan, it is another different story for OPSCC. Most of the Taiwan patients with HPV− OPSCC and many patients with HPV+ OPSCC also have two or all exposures of alcohol drinking, betel quid chewing and cigarette smoking, which all are the risk factors strongly associated with traditional head and neck cancer. Actually, it had been reported that the prevalence of current betel quid chewer and cigarette smoker among men in Taiwan are about 10% and 30%, respectively. Therefore, in clinical practice, comparing to the western countries, we must face more HPV− OPSCC or HPV+OPSCC but combined with cigarette and/or betel quid abuse in Taiwan. And the treatment for OPSCC in Taiwan is definitely more complicated and challenging than Western countries.

In my presentation, I would like to present the clinical characteristics and treatment outcome of OPSCC last decade (from January 1999 to August 2013) in our hospital. A total of 300 eligible patients, including 74 HPV+ patients (38 patients with alcohol/betel quid/cigarette (ABC) exposure and 36 patients without ABC exposure) and 226 HPV- patients, were enrolled. The 5-year disease-free survival rates for HPV- OPSCC patients, HPV+ OPSCC patients with and without ABC exposure were 49.8%, 58.4%, and 94%, respectively. The 5-year overall survival rates for HPV- OPSCC patients, HPV+ OPSCC patients with and without ABC exposure were 46%, 57.4%, and 86%, respectively. The advanced primary tumor (T3/4 classification) and HPV- OPSCC were the independent adverse prognostic factors for both disease-free survival and overall survival. The positive ABC exposure history (≥ 1 item) was the independent adverse prognostic factor for disease-free survival. The exposure history to ABC was the independent adverse prognostic factor for overall survival. In short, Over the past decade in an endemic betel quid region, around half of the HPV+ OPSCC patients had ever consumed ABC. The consumption of ABC had a significant negative impact on 5-year disease-free survival and overall survival.

Tongue conservation treatment by induction chemotherapy followed by surgery and risk-adapted adjuvant therapy for oral tongue squamous cell carcinoma : A phase II clinical trial

以“前導性”化學治療加上手術及輔助治療做舌癌的舌保留手術：第二期臨床試驗

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Background: An open-label, non-comparative phase II clinical trial to assess the efficacy and feasibility of tongue conservation treatment with sequential induction chemotherapy (ICT), tongue conservation surgery and postoperative concurrent chemoradiotherapy (POCCRT) in patients with oral tongue squamous cell carcinoma (OTSCC).

Methods: Newly diagnosed OTSCC patients, cT2-4 N0-2 M0 were recruited after completing the informed consent. The ICT (DCU regimen) consisted of Docetaxel 36 mg/m_2 follow by cisplatin 30 mg/m_2 intravenously on day 1 and day 8, and oral tegafur/uracil 300 mg/m_2/d plus leucovorin 90 mg/d on day 1 to 14, with every 21 days as a cycle. After the first cycle of ICT (DCU1), patients with more than 30% decrease in the longest tumor diameter by physical examination underwent the 2_{nd} cycle of ICT (DCU2). Surgery according to residual tongue induration was done after DCU2 and POCCRT was waived for T2 patients without adverse pathological features. Patients with less than 30% decrease after DCU1 underwent immediate surgery and POCCRT. (ClinicalTrials.gov NCT03161548)

Results: From July 2011 to December 2015, a total of 23 patients were enrolled, and 87% of patients were classified as stage III-IV. Clinical responder of DCU1 was 90.5% (19/21) and 88.2% (15/17) of patients were determined as DCU2 responder, including 7 patients (41.2%) achieved complete response on pathologic examination. Tongue conservation surgery was performed in 16 responders to ICT, including 1 patient who received only DCU1. Pathologic CR (ypT0) was achieved in 8 patients (50%) and only 1 patients had positive margin (6.3%). After a median follow-up of 33.1 months (range 3.1-71.1), only 1 patient developed local recurrence. The 5-year OS (0% vs. 78%, p=0.0009) and DSS (0% vs. 90%, p<0.0001) rates were significantly different between DCU1 non-responders and responders.

Conclusion: Tongue conservation treatment by ICT followed by conservation surgery and POCCRT when indicated is feasible for OTSCC in good responder to ICT. However, the outcome of non-responder is dismal. Further study in a larger patient population is warranted.

Recent advances of organ preservation therapy in head and neck cancer- Boron Neutron Capture Therapy (BNCT): A New Generation of Targeted Charged-Particle Therapy

頭頸癌器官保留性治療的最新進展：新世代標靶性粒子放射治療介紹 - 硼中子捕獲治療

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Radiation therapy plays an important role in standard cancer treatment. However, patients who are resistant to traditional radiation therapy or who have relapsed after conventional radiation therapy are often encountered in clinical practice. There is therefore an urgent need for a new radiation therapy for this type of patient. Although boron neutron capture therapy is not a new concept of radiation therapy, due to technological breakthroughs and conceptual improvements at the start of the 21st century, this therapy, which covers multidisciplinary technologies, such as medical physics, atomic science and technology, boron-containing drug synthesis, radiobiology, and clinical oncology has advanced greatly, and has gradually matured to a clinically useful therapy for patients with cancer.

Since March 2017, Taipei Veterans General Hospital and Nuclear Science & Technology Development Center in National Tsing Hua University have been collaborating to conduct an emergent BNCT model for recurrent head and neck cancer patients. This treatment model is approved by the IRB (Institution Review Board) of Taipei Veterans General Hospital and TFDA (Taiwan's Food and Drug Administration) after special application. Up to now, we already treated for more than twenty recurrent head and neck cancer patients with compassionate use and some patients had good treatment response with less normal tissue toxicities.

Here we'd like to share our clinical experience and hope to promote this unique targeted particle radiotherapy for organ preservation therapy of our head and neck cancer patients.

Recent advance in drug therapy for late staged head and neck squamous cell carcinoma

晚期頭頸癌藥物治療的最新進展

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Advance head and neck squamous cell carcinoma (HNSCC), including locally advanced and recurrent/metastatic diseases, account for most population of all HNSCC patients. Multidisciplinary approach and treatments are now prominent for such disease and the role of drug therapy is now focusing on several major parts: neoadjuvant (induction) chemotherapy, primary concurrent chemoradiation (CCRT) or anti-EGFR monoclonal antibody (cetuximab) combined with radiation (Bio-RT), post-surgical adjuvant CCRT, and palliative cetuximab combined with chemotherapy or immune checkpoint therapy (IO). Interestingly, most new treatment regimens or novel drugs have been developed until recent 15 years. In this speech, a brief introduction of the advance in different parts of drug therapy will be discussed.

The standard triple-combined induction chemotherapy with docetaxel/cisplatin/5-FU was established after two pivotal trials published in 2007. A little difference of regimens exist between these two trials and dosage modulation seems to be necessary in Taiwanese patients. In addition, although further two phase III trials showed there were no survival benefits for induction chemotherapy before CCRT, it is still recommended especially for hypopharynx SCC patients in NCCN guideline. The standard role of primary CCRT was established after a pivotal trial for larynx preservation published in 2003 and a meta-analysis from MACH-NC group in 2000. There is some debate for treatment related complications, which may influence long-term survival in CCRT population from RTOG 91-11 trail. Bio-RT first showed survival benefit in 2006 comparing to RT alone. Because recent two phase III trials demonstrated primary CCRT is still better than Bio-RT in HPV (+) oropharyngeal cancer, it is favorable for CCRT in locally advanced HNSCC patients unless ineligible for chemotherapy. Adding cetuximab with platinum/5-FU regimens showed survival benefits for recurrent/metastatic (R/M) HNSCC in 2008 and IO first showed survival benefits for platinum refractory R/M HNSCC in 2016. Now many clinical trials including IO combination with palliative chemotherapy, CCRT, or novel agents are still undergoing.

Drug therapy for advanced HNSCC is springing up and gives patients more help and better prognosis. On the other hand, there is also more challenge for physicians in treatment planning and side effects managements.

Submandibular gland transfer to reduce post-radiation xerostomia for patients with head and neck cancer

針對頭頸癌病患施行下頷腺移轉來降低放射治療後口乾症狀

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Head and neck cancer is the seventh most common cancer worldwide, the sixth in Taiwan and the ninth in the United States. Up to 90% of head and neck cancer patients receive radiotherapy as primary treatment or postoperative treatment concurrently with or without chemotherapy or targeted therapy.

Xerostomia is the most common serious and long-term adverse effect of radiotherapy for head and neck cancer patients. It affects patients' dental care, taste, mastication, swallow, and greatly influences their quality of life after treatment. Even though the advancement of parotid gland sparing intensity modulated radiation therapy (IMRT), the incidence of moderate to severe xerostomia remains as high as 30-38% at 12 months post-treatment and 22-36% at 24 months post-treatment.

The transfer of submandibular gland to submental space with shielding from radiation was first reported by Jha and Seikaly et al. A systematic review and meta-analysis demonstrated that submandibular gland transfer is effective for xerostomia prevention without serious complications. After 5 years of conventional radiotherapy, the incidence of xerostomia in gland transfer group was significantly lower than in the non-transfer group (15.4% and 76.9%, respectively, $P<0.001$).

In this presentation, we will review the benefit and complication of submandibular gland transfer. Besides, we will introduce how to perform in selected head and neck cancer patients. As an otorhinolaryngologist, we could put our effort to reduce the incidence of post-treatment xerostomia and improve the quality of life for our patients.

Scoring for fiberoptic endoscopic evaluation of swallowing

吞嚥纖維內視鏡檢查之評分研究

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Patients with head and neck squamous cell carcinoma (HNSCC) commonly suffer from swallowing disorders during and after treatment. Most of them felt difficult to swallow or required feeding tube to maintain adequate nutrition. Both modified barium swallow (MBS) and fiberoptic endoscopic evaluation of swallowing (FEES) are useful tools to evaluate and diagnose swallowing disorders and both require a subjective image analysis. The advantages of FEES include easy executing at the clinic and avoiding the use of barium and radiation exposure. Besides, it also detects laryngeal penetration, aspiration as effectively as MBS. However, the scoring and intra-/inter-rater reliabilities remain challenging for FEES. We studied the standardization of FEES scoring by using Penetration-Aspiration score (PAS) and Yale pharyngeal residue severity rating scale (YPR-SRS) in a two stage design, before and after group evaluation and discussion of video recordings by speech language pathologists. The experience and difficulties during the scoring processes will be shared, as well as the way to improve the rating reliabilities. Future directions in optimizing swallow evaluation for HNSCC patients will also be discussed.

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抗藥性微生物時代的新治療選項

New Treatment Options in an Era of Antimicrobial Resistance

時 間：108年6月22日 13:30~17:20

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Taipei International Convention Center

抗藥性微生物時代的新治療選項
New Treatment Options in an Era of Antimicrobial Resistance

Drug-resistant *Pseudomonas aeruginosa*: What are the treatment options left?

抗藥性綠膿桿菌的治療選項

Edsel Salvana

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Pseudomonas aeruginosa is an aerobic, Gram-negative bacillus that displays high level of resistance due to multiple mechanisms: beta-lactamase production, antibiotic efflux, porin alterations, and target site modification. The intrinsic and acquired resistance mechanisms illustrates the therapeutic challenge of *P. aeruginosa*.

Our first main objective is to understand the disease epidemiology, risk factors, and burdens caused by multidrug resistant (MDR) *P. aeruginosa*, as well as the risk attribution of inappropriate treatments.

Additionally, because of the rapid increase in antimicrobial resistance, there is an urgent need for antibiotic stewardship strategies to preserve currently effective resources. We will discuss the treatment strategies that tackle MDR *P. aeruginosa*, including empirical and definitive treatments, monotherapy vs combination, and rationale for de-escalation.

Despite the implementation of antimicrobial stewardship strategies, our currently available antibacterials have become less effective, and there is a crucial need for new agents. Lastly, we will elaborate on the new available treatment options for diseases caused by MDR *P. aeruginosa*, such as complicated urinary tract infections and complicated intra-abdominal infections.

Emerging antimicrobial resistance in Taiwan community

台灣社區新興抗藥性細菌

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Taiwan Surveillance of Antimicrobial Resistance (TSAR) program, conducted by National Health Research Institutes, investigated the resistance in Taiwan community and hospitals. Recently, TSAR found the emergence of fluoroquinolone-resistant pathogens and plasmid-mediated colistin resistance mechanisms, *mcr*-type genes, in the community.

Fluoroquinolone are the third most widely used antibiotic class worldwide, with an average growth rate of 5%. They are highly bioavailable, broad-spectrum agents with activity against Gram-negative pathogens, especially those resistant to other classes of antimicrobial drugs, and relative safety in adults. However, the emergence of resistant strains in recent decades, particularly in hospitalized patients and those with chronic recurrent infections, has compromised their efficacy. This impact can be attributed to the selective pressures of excessive use. TSAR identified increasing fluoroquinolone resistance in Gram-positive and Gram-negative pathogens in the community. The prevalence, mechanisms, and possible reasons of fluoroquinolone resistance in Taiwan will be presented in the part of this section.

Colistin has been considered as the last resort of antibiotics for the treatment of multi-drug resistant pathogens. The resistance had been low due to its unique mechanism of actions. However, in 2015, the gene encoding plasmid-mediated colistin resistance, *mcr*-1, was first reported in *Escherichia coli* from animal meat and humans. The easy mobilization of *mcr*-type genes, low fitness cost, and high agricultural use of colistin may contribute their wide spread worldwide. The second part will discuss the prevalence of *mcr*-type genes in *Enterobacteriaceae* and their molecular characteristics and those isolated from retail meats purchased from traditional and supermarkets in Taiwan.

Update on the current antiviral therapy

抗病毒藥物治療的新發展

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For the treatment of specific pathogens, it is necessary to make a correct diagnosis and obtain useful tools to evaluate the response to treatment. In the past, due to lack of specificity of clinical symptoms, inadequate support from laboratory techniques, and the timeliness of traditional culture methods, accurate diagnosis and early assessment of treatment efficacy in viral infections are usually unsuccessful. Development of antiviral agents has thus been obstacle as well. In recent years, due to the advances in molecular biotechnology, it is possible to timely and correctly diagnose various viral infections. In addition, with the viral load measurement technology becoming more and more mature, monitoring the therapeutic effect becomes feasible in clinical practice. Combining basic researches, new diagnostic modalities, and clinical studies, a better understanding of the pathogenesis of viral infectious diseases is provided. Antiviral agents have emerged for application in clinical treatment of various viral infections, including viral hepatitis, influenza virus, HIV infection, and herpes virus infections. A number of new antiviral agents are also on the market or in the pipeline. Hopefully these developments will bring new insight into clinical treatment of viral infections.

Antiretroviral options for patients with virologic failure

愛滋病毒治療失敗的治療選項

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Since the introduction of highly active antiretroviral therapy (ART) in 1996, the mortality and morbidity of HIV infection has declined dramatically. However, about 20% of virological failure during ART occurs, which lead to drug resistance and poor outcome. Evaluation of virological failure should include an assessment of adherence, drug-drug interactions, drug tolerability, treatment history, and drug-resistance testing results. Drug-resistance testing is recommended to be performed while the patient is taking the failing antiretroviral regimen. A new regimen should include at least two, preferably three, fully active agents. In general, patients who receive at least three active drugs experience better and more sustained virological response than those receiving fewer active drugs in the regimen. These three drugs should be selected based on the patient's ART history and a review of their present and past drug-resistance test results. Active drugs may be newer members of existing drug classes that are active against HIV isolates that are resistant to older drugs in the same classes (e.g., etravirine, darunavir [DRV], and dolutegravir [DTG]). An active drug may also be one with a unique mechanism of action compared to prior therapy in that individual. Increasing data in treatment-naive and treatment-experienced patients show that an active pharmacokinetically-enhanced PI plus one other active drug or plus several partially-active drugs will effectively reduce viral load in most patients. In the presence of certain drug resistance mutations, some antiretroviral agents, such as DTG, ritonavir or cobicistat-boosted DRV, and ritonavir-boosted lopinavir , need to be given twice daily instead of once daily to achieve the higher drug concentrations necessary to be active against a less-sensitive virus. It is also important to provide continuous adherence support to all patients before and after regimen changes.

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婦科及產科疾病之個人化精準治療

The Personalized Treatment of Obstetrics & Gynecology

時 間：108年6月22日　　13:30~17:10

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婦科及產科疾病之個人化精準治療

The Personalized Treatment of Obstetrics & Gynecology

Towards the elimination of cervical cancer

消滅子宮頸癌計畫

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The ultimate of cervical screening

Since the introduction of Papanicolaou test in the 1940s, the incidence of cervical cancer drops significantly in countries where populational cervical screening is organized. Nevertheless, cervical cancer is the fourth leading cancer for women globally. It is estimated that 570 thousand new cases and 310 thousand women died of this disease in 2018.

Cervical cancer has a substantial negative impact on overall quality of life of the affected women and socioeconomic effects on the women as well as their families and communities. In 2010, cervical cancer cost the global economy an estimated USD 2.7 billion. By 2030, this figure is projected to rise to USD 4.7 billion if actions are not taken.

Currently, consistent evidence demonstrates that detecting human papillomavirus (HPV) from cells of cervicovaginal discharge shows higher sensitivity than the Papanicolaou test, and primary HPV testing has been implemented in some countries and regions. Immunization using HPV vaccine before infection prevent most CIN and is generally accepted as the best way for primary prevention of cervical cancer. Seventy (70)-85% reduction of cervical cancer can be reached if HPV vaccination before sex debut is engaged. The un-protected HPV types after immunization are types which associate to a later onset of the high-grade squamous intraepithelial lesion (HSIL) than HPV types 16, 18 or another five types in Gardasil 9.

Under the current circumstance, we propose a cervical screening protocol that may maximize the cost-effectiveness for the low- and middle-income countries: (1) an HPV typing at the postpartum visit to identify women who are at risk of developing HSIL, (2) another HPV typing taken five years later if no HPV detected. (3) once high-risk HPV is detected, confirmation of no HSIL+ then an annual follow-up is indicated. (4) Annual Papanicolaou test for those with HPV infection other than type 16 or 18. Self-sample collection for HPV detection may attract those who are unwilling to attend the cervical screening and an easy-to-use collection kit for this purpose is welcome.

Big data and precision medicine

大數據與精準醫療

Kuo-Hu Chen

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In the past, diseases were diagnosed based on existing medical knowledge as well as physicians' experiences, and were treated according to medical guidelines. The patients who were affected by the same disease usually undergoing the same treatment, including medication and surgeries. However, the individual differences, such as genetic variants, body constitution, and personal response to treatment are not considered. Nowadays, new concepts and techniques have changed the world with the development of internet of people and things, information technology, big data and next generation genome sequencing. Disease-centered therapy has been shifted to patient-centered therapy. The development of translation medicine and next generation genome sequencing facilitates the understanding of a disease from a clinical to molecular level. On the other hand, the big data helps clinicians and patients make decisions which conform to personal requirement. Therefore, the treatment of diseases has progressed from medical guidelines (one for all) to personalized medicine (all for one).

Good examples of big data are the Taiwan Biobank, and the National Health Insurance Research Database (NHIRD), both of which recruit a large population rather than retrieve smaller samples from the target population. Thus the errors and bias from a sampling process are minimized. The application of internet of people and things and information technology makes it possible to solicit big data for trend studies and further analyses. In brief, precision medicine is an emerging approach for disease prevention and treatment that takes into account people's individual variations in genes, environment, and lifestyle. With the developments of internet, information technology, big data and genome sequencing, precision medicine can be achieved for prediction of diseases as well as making decisions.

Non invasive prenatal genetic diagnosis and liquid biopsy

非侵入性產前遺傳診斷與液態生檢

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Reproductive genetics, as well as cancer genomics, are two foremost tiers of “Precision Medicine”. Due to the booming of the cell-free DNA based testing, both cell-free fetal DNA (cffDNA) and cell-free tumor DNA (ctDNA) now have achieved huge success with the advancement of next generation sequencing technologies and platforms, as well as the bioinformatics analytical pieplines. However, despite very challenging and much more lagged behind, cell-based liquid biopsy, such as platforms isolating and capturing circulating fetal cells (CFCs) and circulating tumor cells (CTCs) is emerging by a few more reliable diagnostic facilities. The merge of DepArray and Cell Search by Menarini and Silicon Biosystems marked the milestone of CTC-based liquid biopsy. In this talk, the speaker will briefly summarizes the recent advances as well as the current status of liquid biopsy in cancer research, as well as the rapid intake of non-invasive prenatal testing based on cell-free DNA technologies, and tries to present this topic by perspective of not just a user, but a developer of bioinformatics algorithyms, test validation/acceditation, and even hardware manufacturing.

Precision medicine in obstetric care, especially in pre-eclampsia

產科精準醫療 , 以子癲前症為例

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Pre-eclampsia is defined as pregnant woman who has gestational hypertension plus proteinuria or multiple organ dysfunction after 20 gestational weeks. The incidence is 2-5%, but it is the leading cause of perinatal mortality and morbidity all over the world and a life threatening disease especially when it occurs early in pregnancy or has been delayed diagnosed or inappropriately treated.

Although it's actual mechanism is still not clear. Abnormal syncytiotrophoblast invasion and endothelial dysfunction are believed to be two major pathogeneses. Many known factors are noted to contribute to its occurrence. The maternal genes including PAI-1 (rs1799889), HLA-G (rs66554220), IL-6 (-572G/C, -597G/A, and -174G/C), VEGF, -634G/C (rs2010963); Flt-1 (rs3025039, +936C/T) and IL-10 (-592A/C) and fetal genes including HYP2, DSCR3, RASSF1A have been cloned out. And some immunologic factors, eg sFlt- 1/PIGF; sEng, PAPP-A, PP-13; IL-6, IL-8, FGF2, IGF-1; MMPs; NSE are reported linked to pre-eclampsia. Even the deficiency of Vitamin D3 is also a causing factor. And there are some well known risk factors, eg. history of pre-eclampsia in previous pregnancy, chronic hypertension, overt/gestational diabetes mellitus, autoimmune disease, renal disease, obese, nulliparity, maternal age 35 years or older, and multifetal gestations. No single one factor could efficiently predict the pre-eclampsia.

The detection rate of early pre-eclampsia is more than 90% when combine 1st trimester uterine artery PI or RI > 90 percentile, PAPPA, PlGF, and maternal mean arterial pressure. The actual risk is still low with a cut-off value of 1/200 to recommend long term use of aspirin with 80% efficacy to pregnant women. However, most of them did not develop pre-eclampsia even not taking medicine. In 2016, NEJM reported that sFlt-1:PlGF ratio cutoff < 38 at 24-36 gestational weeks had a negative predictive value of 99.3% (95% CI, 97.9 to 99.9), with 80.0% sensitivity (95% CI, 51.9 to 95.7) and 78.3% specificity (95% CI, 74.6 to 81.7). However, the positive predictive value of an sFlt-1:PlGF ratio ≥ 38 within 4 weeks was only 36.7%. Thus there is an emergency need to develop some models to precisely predict the pre-eclampsia and also provide an effective treatment.

Endometrial cancer screening: Time to revisit

子宮內膜癌篩檢：是時候重新思考了！

Hung-Cheng Lai

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The increasing incidence and mortality of uterine and ovarian cancer in Taiwan during the past 4 decades suggests an emergent need of new strategies. Considering methylation assays are promising in detecting endometrial cancer (EC) noninvasively, we investigated the annual numbers of new EC and invasive procedures (IVP) to estimate how many IVP would be spared if a methylation assay was introduced for triage.

We conducted a nationwide survey based on data from National Health Insurance (NHI) Research Database in Taiwan and the Taiwan Cancer Registry. Between 2009 and 2014, women undergoing IVP were enrolled, including endometrial sampling, diagnostic dilation and curettage, hysteroscopy, hysteroscopic removal of polyp and hysteroscopic myomectomy. Those with a diagnosis of infertility were excluded. The numbers of new EC and IVP in each year were calculated and stratified by age: <40 years old, 40-49 years old and ≥50 years old. A methylation assay detecting EC by cervical scrapings reported a sensitivity of 91.8% and a specificity of 95.5%. The performance of the assay was simulated based on the 2014 NHI data. In Taiwan, the younger the women, the more IVP required to diagnose one EC.

We demonstrated at least 90% of IVP were spared if a noninvasive test using methylation markers was introduced for triage, which minimized risk of IVP. A molecular Pap detecting aberrant DNA methylation for endometrial cancer is promising.

Sentinel lymph node mapping in endometrial cancer

子宮內膜癌哨兵淋巴結之對映取樣

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The “precision” or “personalized” medicine has been the strategy to improve efficacy through target therapy in medical oncology. The similar concept at precision is starting in surgical oncology. Sentinel lymph node (SLN) mapping has been advocated into the alternative surgical staging of endometrial cancer to reduce morbidity associated with a complete lymphadenectomy.

In a multi-center, prospective, cohort study with a comparison of SLN biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial), clinical stage 1 endometrial cancer of all histologies and grades undergoing robotic staging. SLN identified with indocyanine green (ICG) have a high degree of diagnostic accuracy in detecting endometrial cancer metastases and can safely replace lymphadenectomy in the staging of endometrial cancer. The Society of Gynecologic Oncology’s (SGO) Clinical Practice Committee and SLN Working Group also reviewed the current literature for the preparation of this document. These articles included techniques of SLN mapping in endometrial cancer, pathology and clinical outcomes from SLN assessment and evidence-based recommendations for the inclusion of SLN assessment in the treatment of patients with endometrial cancer.

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台灣重大交通事故回顧及骨折微創治療之新進展

Review of Taiwan Disastrous Traffic Accidents and Advance in Minimally Invasive Surgery of Orthopaedic Trauma

時 間：108年6月22日 13:30~17:30

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Taipei International Convention Center

台灣重大交通事故回顧及骨折微創 治療之新進展

Review of Taiwan Disastrous Traffic Accidents and Advance in Minimally Invasive Surgery of Orthopaedic Trauma

Analysis of causalities in Puyuma derailment accident

普優瑪火車出軌事件傷亡的分析

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Puyuma express train derailment incident happened at 16:50 on 21 Oct. 2018, which the service 6432 express from Shulin bound for Taitung, derailed on a curve with a radius of 300 metres when passing through the Xinma station in Yilan County, there were 366 passengers travelling on the train. Of the eight carriages, numbers 3 through 8 toppled over and collided into each other in a "W" shape, while the rest went off the track with lesser damage. At least 18 people were killed in the accident, with another 215 injured, all on board. According to reports, six of the dead reportedly were under the age of 18. The Health Ministry confirmed that 53 injured remained in the hospital. Most victims were sent to Yilan hospitals, mainly 37 people for Luodong Sant Mary Hospital, 64 people for Luodong Pho-Ai Hospital, 47 people for Suao Veteran Hospital, 5 people in National Yang Ming University Hospital, 1 person in Yilan Renai Hospital, The remaining 36 people were sent to Taipei or Hualien and Taitung Hospital after initial treatment. We examined the victims in Yilan, the ages were from 4 to 75 years, with an average age of 41 years for man and 47 years for woman. The passengers with the most serious injuries are located in the front carriages. Most of victims suffered from soft tissue contusions and lacerations involving the trunk and limbs. According to the record of registration, 21 patients, the average Abbreviated Injury Scores (AIS) score of them was greater than 20 points, and 12 patients had fracture of extremities and spine. Among the casualties, there were only 4 serious visceral blunt injuries. All the patients who were admitted and treated in Yilan were properly cared and discharged smoothly.

Orthopaedic managements for victims in Puyuma derailment accident

普悠瑪火車出軌傷患骨科處理的經驗

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Puyuma derailment accident, happened in the evening on Oct. 21, 2018, is the most severe event in Taiwan Railways. According to the official report, there are 18 victims dead in this accident. Besides, 279 passengers had injuries. Our hospital is the Level-I emergency trauma center in the Yilan county. We activated the emergency procedures for this disaster immediately. We cooperated with EMT system at the scene and offered the medical managements.

There were 63 injuries passengers sent to our emergency department. 43 of 63 patients were discharged under stable situation after initial managements including change dressing, pain control, or simple wound suture. Nineteen of 63 patients were admittion for further evaluations and managements. Unfortunately, 1 of 63 patients underwent the CPR procedures due to OHCA. One of 63 patients was transferred to VGHTPE under the request.

Most of the victims had the laceration wounds over the head, face, trunk or extremities. They also had suffered from the contusion or blunt injury. Among the admissions, four were taking care in the ICU because of the severity of injury including head injury with ICH and SAH, multiple ribs fractures with hemopneumothorax and acute respiratory failure, and liver laceration with bleeding. The other victims were admitted to ordinary ward and monitored the vital signs closely. There were cervical fracture, pelvis fracture, sacral fracture, hip dislocation, tibia and fibular shaft fracture, facial bone fracture, and simple rib fracture. After the initial resustations, we performed the surgery procedures by subspecialist next day.

There are more than two hundred volunteers came back to hospital for helping the patients at that night. They are doctors, nurses, technologists, pharmacologists and social workers. The experience in our hospital showed the ability in the major trauma managements.

Analysis of mechanism of injury in derailment accident: Is there any method to decrease causalities?

火車出軌意外骨科病患受傷機轉的探討：是否有方法可以降低傷害？

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Train accidents can be divided into collisions and derailments, the mechanisms of injury between them are different. In frontal train-to-train collisions, passengers may hit seats, tables or objects in front of them, so head and chest contusion are the most common injuries. In contrast, train derailment produces a different pattern of injuries from that seen in a train collision, derailments can generate a large lateral deceleration when the car rolls onto its side and impacts the ground. The interior of train may present a potentially hostile environment under such circumstances. Train crash injuries frequently result from impact with interior surfaces not designed for occupant contact. These injuries are exacerbated during a “farside roll”. Most patients who were seriously injured or killed had been sitting in the carriages which had jack- knifed. Victims from Puyuma express incident described their feeling as though they were in the revolving drum of a washing machine, being thrown both forward in the carriage and against the floor, roof. Many people said that they had been injured by the metal and wooden seat frames from which the padding had come off. Some were thrown through the train windows to land beneath the carriage. Many said that they had been hit by unrestrained luggage and other passengers. Improvements in the design of carriage interiors may reduce morbidity. Such as the design concept of compartmentalization, rearranging seats and restrain barriers to form a protection zone around occupants’ luggage had been stored in lockers. The padding of seats must be securely fixed, and carriages may not hold large areas of glazed window for the safety of passengers.

Amputation or Reconstruction? A case of bilateral catastrophic legs underwent salvage treatments: Strategies in plastic surgery for mangled limbs

截肢或重建？對於災難性毀損肢體病例的救治：整型外科治療策略

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High-energy related lower limb trauma usually leads to extensive soft tissue, bone and vascular injury. The function of limbs was severe impaired. Patients usually have other combined injury at head or trunk area. It is difficult to make optimal treatment for patients with mangled limbs. Primary amputation and prosthesis fitting decrease duration of hospitalization and achieve ambulation earlier. The disadvantages are including neuromas, stump problems and derangement of body image. Reconstruction can preserve patients' nature limbs but has high complication rates, high costs and variable functional outcome. Some patients need delayed amputation. When patients have associated life-threatening injuries, long ischemia time or extended tibia bone injury, immediate reconstruction or replantation is not suggested. For better long term outcome, a functional sole of the foot is the goal in lower limb reconstruction. To achieve this goal, the plantar organ should be anatomically intact and reliable innervated.

Amputation or reconstruction? A case of bilateral catastrophic legs underwent salvage treatments: Strategies in orthopaedic surgery for mangled limbs

截肢或重建？對於災難性毀損肢體病例的救治：骨科治療策略

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The definition of mangled extremity is a limb with an injury affecting at least three out of four systems including soft-tissues, underlying bone, nerves, and vessels. The data regarding management of mangled limb are conflicting and without Class-I evidence in the literatures. There is no any score able to be used as the sole criterion by which amputation decision is made.

The authors reported a case who sustained catastrophic injuries from the traffic accident. While the proper ATLS protocols were being underway, the bleeding was controlled with direct pressure, tourniquet, and compressive dressing for the bilateral mangled lower limbs. But the secondary survey in the ER was not advantage. Thus, the patient was then immediately sent to the operating room for further exploring. After evaluation of both the orthopaedic and plastic surgeon, consensus was reached on salvage treatments. In the orthopedic strategies, damage control was on the first stage, followed by subsequently reconstruction surgeries.

Wether amputation or not, maybe none of these two options for a mangled limb concludes in a satisfactory result. Any of both therapeutic alternatives has disastrous physically or emotionally impact on the patient.

Arthroscopic reduction minimally invasive surgery for ankle fractures

以關節鏡輔助復位踝關節骨折微創手術

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Open reduction with internal fixation (ORIF) remains the standard treatment for ankle fractures. However, wound complication rates have been reported up to 30% with standard ORIF, including infection, wound dehiscence, and hardware irritation. Among these complications, the incidence of infection following ORIF of ankle fractures varies from 1.4% to 13.1% in the current literature.

As an emerging trend in orthopedic traumatology, few articles describe new techniques of minimally invasive surgery (MIS) for fixation of lateral malleolar fractures in an effort to decrease the wound complications. These reports using a single or mixed MIS technique in limited numbers of patients achieve satisfactory surgical outcomes with low complication rates.

In addition to wound complications after ORIF for ankle fractures, poor functional outcomes are reported consistently even with anatomical reduction of bony structures, possibly due to invisible and untreated intra-articular lesions. For this reason, arthroscopy has been used in acute ankle fractures for accurate detection of intra-articular lesions, such as syndesmotic injuries and osteochondral lesions.

We established an algorithm of arthroscopic reduction and minimally invasive surgery (ARMIS) for supination-external rotation (SER) fractures: MIS for lateral malleolar plating, concomitant arthroscopic evaluation of syndesmosis, and arthroscopic assisted reduction of medial malleolar fractures.

ARMIS can achieve satisfactory reduction of ankle joint with encouraging surgical outcomes. It is a safe and reliable alternative treatment for ankle fractures with a lower incidence of complications.

Arthroscopic approach for treatment of distal clavical fracture/ AC joint dislocation

以關節鏡治療遠端鎖骨骨折 / 肩鎖關節脫臼之微創手術經驗

En-Rung Chiang

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Acromioclavicular joint dislocation is very common injury to the shoulder girdle. It remained controversial whether type III injury needed operative intervention. Varied procedures with varied clinical results had been advocated to treat this clinical scenario. In the past, open techniques including hook plate and screw fixations remained the mainstream of procedures. However, arthroscopic approaches with reasonable results were reported in recent years. Here we present our preliminary experience in treating type III acromioclavicular joint dislocation with arthroscopic coraco-clavicular ligament reconstruction.

Minimally invasive surgery in thoracolumbar fractures

胸腰椎創傷性骨折微創治療之新進展

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Background: The role for minimally invasive surgery (MIS) continues to expand in the management of spinal pathology. In the setting of trauma, operative techniques that can minimize morbidity without compromising clinical efficacy have significant value. MIS interventions further enable earlier mobilization, decreased hospital stay, decreased pain, and an earlier return to baseline function when compared with traditional techniques

Methods: Select examples of MIS procedures include percutaneous segmental fixation, vertebroplasty/kyphoplasty, and mini-open lateral access corpectomy/fusion, enabling a less destructive method of fixation and stabilization with limited adjacent tissue destruction. Moreover, proper use of these techniques has been shown to shorten hospital and recovery times, as well as reduce blood loss and perioperative complications. In this study, we summarize the techniques, controversy, and indications for the use of minimally invasive procedures in traumatic spine injuries.

Results: A variety of techniques have been developed as minimally invasive spinal instrumentation has evolved. Prospective randomized studies remain scarce as it relates to the spine-injured trauma population due to the historic follow-up difficulties. Long-term assessment will continue to advance the implications and applications of MIS techniques in the treatment of the spine-injured patient population.

Conclusion: Minimally invasive techniques provide viable options for patients who have suffered traumatic injury to the spinal column. The goals of surgical intervention remain the same as those used when performing open procedures. However, with lessened perioperative morbidity, there comes early postoperative mobilization and rehabilitation.

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發展行動化、客製化及精準化之病人術後止痛研討會臺北榮總60周年院慶暨北區麻醉月會

Postoperative Pain Management: The Development of Patient-focused, Multimodal, and Exquisite Precision Medicine

主辦單位：中華醫學會
協辦單位：臺北榮民總醫院麻醉部、臺灣麻醉醫學會

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Taipei International Convention Center

發展行動化、客製化及精準化之病人術後止痛研討會
臺北榮總60周年院慶暨北區麻醉月會
Postoperative Pain Management: The Development of Patient-focused, Multimodal, and Exquisite Precision Medicine

Past, present and future of pain management service at Taipei Veterans General Hospital

臺北榮總病人術後止痛的經驗與未來發展

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Acute pain management is a global issue. Free from pain is a fundamental human right. Since the start of pain management team in Taipei Veterans General Hospital, we have dedicated our services to improve post-operative pain management with patient control analgesia, multi-model analgesia and interventional nerve blocks. We also incorporate interdisciplinary services to provide mobile, individualized pain management for the future acute pain service.

The trajectory analysis of acute postoperative pain: Development of tailored-patient controlled analgesia and software for Asia population

疼痛軌跡分析：以臺北榮總病人止痛治療大資料庫，發展適合國人的客製化自控式止痛服務與軟體

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For a long time, anesthesiologists focus on the acute pain management after surgery. Well controlled postoperative pain helps to decrease harmful acute effects (i.e., increasing heart rate, high blood pressure, etc.) and facilitate recovery during immediate postoperative period, and long term after discharge from hospital. Because patient-controlled analgesic (PCA) has been proved as a safe and effective management for acute pain, it becomes popular and well-accepted methods worldwide. PCA device allows patients to deliver small analgesic dose when they feel pain. Although the invention of PCA was already for more than thirty years, the quality of care was not improved. One of the reasons is the wide range of heterogeneity between individuals and surgeries. Furthermore, the recommended dosages in the textbook are derived from western country, which is not suitable for Asia population. How to use big data to derive local parameters for tailored patient-controlled analgesia is important. In this speech, we will approach this issue by statistical models and software development in a different view of point.

Innovative intra-needle ultrasound transducer facilitates thoracic regional anesthesia

微型化針內超音波於胸腔麻醉與疼痛治療之發展與應用

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Regional anesthesia in thoracic region is commonly used for analgesia in thoracic surgery and pathology. It is commonly used with different approaches such as thoracic epidural, intercostal nerve block (ICNB) and paravertebral block (PVB). However, during epidural anesthesia, ultrasound-guided ICNB or PVB, tracking the tip and trajectory of needle could be difficult. Using porcine model, we tested an innovative method for thoracic epidural, PVB and ICNB using an intra-needle ultrasound (INUS) transducer as image guidance.

Precision: The current development of neurological interventional pain management for postoperative pain

急性疼痛精緻化：神經系統介入性疼痛治療的現在發展

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With the advancement of ultrasound resolution and usability, interventional acute pain management (regional anesthesia/neuropathy) could be performed in a safer and faster environment than ever before. Under the advantages and principles of multi-modal analgesia, providing more accurate and high-tech postoperative analgesia can promote the postoperative recovery quality of patients and enhance the professional value of anesthesiologists.

Interventional pain practice: Challenges and chances for young physicians

介入性疼痛處置：年輕世代的挑戰與契機

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Interventional pain medicine and regional anesthesia have been very crucial fields in chronic pain management and perioperative care, respectively. In the future years, these interventional techniques and knowledge would still be of paramount importance in medical and surgical care. Since the practice in these fields demand high-level handicraft and the learning process would probably gain some risk to the patient, the critical point comes to: how could we pass on the knowledge and experiences from generation to generation, and achieve a more comprehensive development of pain medicine?

As an young pain physician, Dr. Donald Tang has devoted himself into pain medicine since his late residency in anesthesiology. He initiated his pain clinic in Taichung Veterans General Hospital in 2017, when he was a chief resident. In recent 3 years, he attended to several international meetings and was certified as FIPP (Fellowship of Interventional Pain Practice) in Jan. 2019. During the 3-year period, he encountered certain difficulties, which are probably exclusive for young-generation physicians. In this meeting, he would share the stories to us and told us how did he try to overcome those difficulties for young physicians.

An innovative intra-needle ultrasound system for anesthesia puncture positioning guide

針內超音波系統應用於麻醉穿刺定位導引

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Intercostal nerve block (ICNB) and paravertebral block (PVB) are commonly used for analgesia in thoracic surgery and pathology. During ultrasound-guided ICNB and PVB, the tip and trajectory of the needle could be difficult to trace. We developed an intra-needle ultrasonic (INUS) system assisting anesthesia positioning; apply to PVB, ICNB, Epidural anesthesia (EA), and other puncture applications.

During the puncture, the large angle between the puncture needle and the extracorporeal ultrasonic transducer cause the ultrasonic image of the needle tip is blurred. INUS system can solve the problems above by displaying the distance between the tip and the target.

INUS successfully identifies the tissue layers during the puncture. Using pleural INUS signal as a landmark, thirteen-fourteenths attempts of ICNB and five-sixths PVB were successfully done by non-medical students and confirmed by an experienced anesthesiologist.

INUS is a promising tool for ICNB and PVB by identifying structure in high resolution while inserting the needle. Since it monitors the anatomy from the needle tip, it enables a new approach and evaluates enhance the safety and success rate of the anesthesia.

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乳房整形及重建手術論壇

The Forum of Aesthetic and Reconstructive Breast Surgery

時 間：108年6月22日　　13:30~17:30
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乳房整形及重建手術論壇

The Forum of Aesthetic and Reconstructive Breast Surgery

Autologous reconstruction after oncological breast surgery

針對乳房內上緣之整形式乳房腫瘤切除手術

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Nowadays, surgical excision is still the important part of breast cancer management, and there are usually variable defects left in the breast, which could result in deformed breasts. Therefore, volume replacement is very useful for post-mastectomy reconstruction, especially in Taiwanese patients who have relatively small breasts. This presentation will discuss all the factors which may influence the choices of autologous reconstruction. In the partial mastectomy group, pedicle LD, TDP, LICAP, or LTP flap can be considered if the tumor located center to laterally; and free perforator flap shall be considered if the tumor located medially. In the total mastectomy group, pedicle LD flap may be used if the patient had small and non-ptotic breast; free TUG, LAP, or SGAP flap may be considered if small to medium sized breast; and free ms-TRAM or DIEP flap would be suggested if medium to large breast. Volume of breast is evaluated with 3-D camera, and the volume match is estimated by manual pinch test. The perforators and pedicles are evaluated by contrast CT scan and hand-held doppler. Flaps other than those mentioned or free style perforator flaps may be considered regarding to aesthetic demand of the patient

Endoscopic assisted total mastectomy with immediate reconstruction: Techniques and pitfalls

內視鏡輔助乳房全切除及立即乳房重建

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Endoscopy assisted breast surgery, using minimized axillary and/or periareolar skin incision, which offers better visualization for operation field and allows meticulous manipulation of soft tissue, lead to less skin and nipple necrosis, accordingly it could facilitate immediate reconstruction and resulting to better cosmetic outcome. Furthermore, due to restricted working space and highly techniques depending factors, the operation period and complication's rate could be varied. Thus, for endoscopic assited mastectomy with immdiate breast reconstruction, a meticulous preoperative planning and organization is mandatory to reduce surgical handicaps. Furthermore, well-trained surgeon regarding to details of endoscopic assisted mastectomy will attribute to better surgical results and minimize complication's rate.

Constricted lower pole breasts

如何矯正乳房下緣不足

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Constricted lower pole (CLP) breasts represent a wide range of deformities. Characteristics such as narrow base width especially in lower pole, constricted parenchyma, tight and short inframammary fold (IMF), thickened deep subcutaneous and (or) pectoralis fascia are common. These characteristics can occur singly or in various combinations, so constricted lower pole (CLP) breasts represent a wide range of deformities. Achieving optimal augmentation results in breasts with a constricted lower pole requires that surgeons have a detailed knowledge of the anatomy and implant–soft tissue dynamics that are unique to a constricted lower pole (CLP) breast. Suboptimal outcomes occur frequently following augmentation of these breast types when surgeons apply routine augmentation principles. In this session, the surgical techniques for correction of constricted lower pole breasts will be presented.

The scenario of ptotic breasts correction by using breast implants

如何利用義乳矯正乳房下垂

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Ptosis of breasts is usually corrected by mastopexy or augmentation mastopexy.

Standard surgical correction for ptosis need gland reduction combined with skin resection. However, the patient will be hesitated for the scar problem or visible scar to do such kind of treatment. Review of ideal breast shape and current treatment trend was also made. Implant is for volume replacement of upper pole area. In one stage correction of ptosis, implant pocket and ptosis of gland should be treated in separated plane.

Implant placement for ptosis correction is a compromised method for aesthetic improvement.

Contents:

- ptosis of breasts-nipple ptosis, glandular ptosis, peudoptosis
- ptosis classification- regnault
- ptotic breast surgical treatment
- mastopexy
- augmentation + mastopexy
- implant selection and plane of indwelling
- surgical design for implant only (requested by patient)
- complication

Skin envelope management in reduction mammoplasty

缩乳手術中如何處理皮膚

Ju Young Go

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There are many forms of breast surgery. However, there are 2 main categories, based on whether skin envelope management is needed or not needed. If the skin envelope management is not needed, the main problems are breast volume and shape. If the volume is insufficient, a fat graft or the implant will be added, and if volume reduction is needed, liposuction is done. If the breast shape is abnormal after the implant insertion, we could change it.

In general, skin envelope management is required for the correction of the malposition and asymmetry of NAC (nipple areolar complex), and any kind of ptosis. Skin redundancy and laxity are the also a main reason. The redundant and usually ptotic skin envelope must be reduced in a manner that creates a pleasing shape and yet minimizes and hides the resulting scar most ideally. Traditionally, if the NAC is not lower than the mold, the correction of breast ptosis requires a NAC lift within 3cm, and does not require a significant envelope management. In this case, a periareolar lift should be performed. If the NAC is lower than the mold or if the NAC needs to be lifted by more than 3cm, circumvertical lift and SPAIR or Inverted T lift would be needed for excessive skin removal.

If the patient wants to increase volume, keep it the same, or decrease volume, then the breast design can be adjusted based on the situation. If we insert the implant or remove the implant, we sometimes reduced the vertical scar due to reduced skin redundancy and increased skin laxity. The breast reduction is not also fundamentally different from mastopexy. Its technique is largely divided according to which pedicle is selected and the shape of the final scar. Selection of technique depends on breast size, estimated resection volume, breast shape and surgeon's overall experience.

Regarding breast enlargement, the volume desired by patients with mastopexy or breast reduction varies from patient to patient, often with previous surgical history, and even with acceptable scar size or length. After identifying the patient's needs through sufficient consultation, a variety of short scar techniques, which have more advantages than traditional methods, will be used on the patients. These techniques have been modified in recent years, so a variety of design needs should be applied to enhance the patient's satisfaction.

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最新心室性心律不整之處理

State of the Art Management of Ventricular Arrhythmia

協辦單位：中華民國心律醫學會

時 間：108年6月22日　　13:30~17:30
Time：June 22, 2019　　13:30~17:30

地 點：台北國際會議中心 101C 會議室
Place：Conference Room 101C
Taipei International Convention Center

最新心室性心律不整之處理

State of the Art Management of Ventricular Arrhythmia

Cellular electrophysiological characteristics of ventricular arrhythmia

心室性心律不整的細胞電生理特性

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Ventricular arrhythmias (VA) are responsible for the majority of sudden cardiac deaths, which could be happened in patients with or without structural heart disease. Right ventricular outflow tract (RVOT) is an important focus for the occurrence of ventricular tachyarrhythmias, such as idiopathic ventricular tachycardia (VT), ventricular arrhythmia with Brugada syndrome, and torsade de pointes.

RVOT cardiomyocytes have distinct electrophysiological characteristics with longer action potential duration, larger intracellular and sarcoplasmic reticulum Ca^{2+} content. RVOT in chronic kidney disease has increased Ca^{2+} leak and a higher VT inducibility, which is suppressed by the inhibitors of Na^{+}/Ca^{2+} exchanger, Ca^{2+}/calmodulin dependent protein kinase II, and protein kinase A. Heart failure or metabolic stress enhances RVOT arrhythmogenesis through modulating electrophysiological characteristics and Ca^{2+} homeostasis. In drug-induced Brugada syndrome model, concordant increase in in post-pacing beat action potential duration and contractility leads to the genesis of RVOT VT, which is suppressed by Na^{+}/Ca^{2+} exchanger inhibition.

In conclusion, functional dynamics and regional heterogeneity in electrophysiological characteristics and Ca^{2+} homeostasis contributes to RVOT arrhythmogenesis.

Experimental model of ventricular arrhythmia

心室性心律不整之動物模式

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國立陽明大學 醫學院

Three animal models of electrical storm will be discussed in this lecture:

Global ischemia-induced post shock early VF recurrence model and the role of Cai-mediated REFD (repetitive endocardial focal discharges)

Failure of defibrillation due to early VF recurrence that induced by subepicardial source of rapid activation arising from the interventricular septum. The REFDs existed in early VF recurrence after successful defibrillation. REFDs at the LV endocardium are important for both VF maintenance and post shock recurrence during prolonged GI.

Pretreatment of BAPTA-AM, a calcium chelator, is proposed to suppress the genesis of REFDs and pacing-induced ventricular arrhythmia during GI. This indicated that intracellular calcium dynamics is important in the maintenance of REFDs during prolonged VF.

Pacing-induced HF model and role of SK channel (IKAS)

Spontaneous VF and shortening of APD may be involved in fibrillation-defibrillation episodes in failing ventricles. A study by Chua and Chen et al. (Circ Res. 2011) proposed apamin-sensitive small-conductance Ca2+-activated K+ (SK) channels may be in part responsible for post shock APD shortening. The apamin-sensitive K+ current (IKAS) play a little role in APD regulation in normal ventricles. Failing ventricles on the other hand may rely on IKAS to shorten the APD in situations of intracellular calcium overload.

CAVB_Long QT_VF_Defibrillation model and role of CaMKII

Tsuji et al. (Circulation 2011) reported 53% of complete atrioventricular block (CAVB) rabbits with implantable cardioverter-defibrillator (ICD) subsequently developed ES. ES rabbits showed LV functional deterioration along with prominent alterations in phosphorylation of multiple proteins including CaMKII, Cav1.2 (L-type Ca2+ channel α-subunit), RyR2, and phospholamban, which found similar in some human and animal modes of HF studies. This suggests an insight of ES and potential implication for clinical management. Antagonism of adrenergic activation of CaMKII may account for the beneficial actions. A Ca2+/calmodulin interaction inhibitor (W-7) also showed effective in suppressing ES. Interventions targeting the Ca2+/calmodulin/CaMKII system may prove highly beneficial in preventing both further arrhythmic episodes and hemodynamic deterioration in ES patients.

The anatomic basis of ventricular arrhythmias

心室性心律不整的解剖學基礎

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Catheter ablation has been proved to be an important therapeutic option to treat a variety of cardiac arrhythmias. The efficacy and safety of this technique highly depends on the understanding the characteristics of ventricular structures. In addition, thorough review of the substrates of both ventricles can provide the mechanistic insight into the pathophysiology of arrhythmias.

In this presentation, I will discuss the clinical relevance of critical ventricular structures with the arrhythmogenesis of ventricles. The detailed knowledge of myocardial substrates is essential to decide where and how to ablate the arrhythmias. I would also like to summarize and underscore the important knowledge to be borne in mind while examining the fascinating anatomy of the human ventricles.

Electrocardiographic assessment of premature ventricular complexes and nonsustained ventricular tachycardia in structurally normal heart

結構正常心臟的期外收縮和非持續性心室頻脈的心電圖評估

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The electrocardiographic (ECG) QRS morphology of premature ventricular complexes (PVCs) and nonsustained ventricular tachycardia (VT) has been used to identify the sites of origin and even to predict their clinical significance. The ability to localized or, at the very least, regionalize the sites of origin of PVCs/VT enables the electrophysiologist to concentrate mapping to a specific region. The origin of PVCs/VT may come from any part of right/left ventricular in structurally normal heart. Common sites of origin included right/left ventricular outflow tract, left anterior/posterior fascicule, left coronary cusp, papillary muscle.

Although several factors limit the ability of the QRS patterns to localized ventricular arrhythmia (VA) origin, including presence and size of infarction, degree of intramyocardial fibrosis, the shape and orientation of the heart, and influence of nonuniform anisotropy in affecting propagation from the site of the tachycardia, etc. Despite these limitations, the ECG still remains a useful tool to assess the location of ventricular arrhythmia and provide clinical information in the structurally normal heart.

Some features are helpful in localizing the PVCs/VT from the QRS, including (1) QRS width, (2) QRS axis, (3) bundle branch block pattern, (4) precordial concordance, (5) precordial transition, and (6) presence of QR pattern. The site of origin affects QRS width: septal VAs generally are narrower than those from the free wall. The QRS axis is related more to the superior/inferior activation of normal muscle. The bundle branch block pattern is related to the sequence of right and left ventricular activation. Precordial concordance of the QRS reflects precordial leads having a. similar morphology, either all positive or all negative. Positive concordance is seen only in VAs arising at the base of the heart. Conversely, negative concordance is seen in VAs originating near the apical septum. Finally, the presence of QS pattern means myocardial activation away from the site recording the QS complex.

The surface 12-lead ECG is an important and useful tool for localization of PVCs and nonsustained VT site of origin. While it has some inherent limitation, it remains indispensable in the overall clinical and procedural strategy for managing patients with these ventricular arrhythmias.

The application of cardiac image to evaluate ventricular arrhythmogenesis in structural heart disease

心臟圖像在結構性心臟病心室性心律失常中的應用

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Ventricular arrhythmia (VAs) is a major cause of sudden cardiac death and mortality in patients with structural heart disease. Echocardiography is the most commonly used techniques for evaluation of cardiac and structures and functions. With the improvement of imaging technology in recent decades, multimodality imaging has become the mainstream in managing patients with VAs. It not only plays a role in determining the etiology, but also identifying potential pathogenesis, and providing prognostic significance. The spectrum of cardiac imaging could involve echocardiography, nuclear imaging, multidetector cardiac computed tomography, cardiac magnetic resonance imaging, and even PET scan. For example, the presence of myocardial scar creates circuits of reentry, which could only be detected via invasive electrophysiology study in the past. Nowadays, imaging technology has enabled detailed characterization of the arrhythmogenic substrate with increasing precision and detection of reentry circuit before intervention. That is, the role of cardiac imaging has expanded from a diagnostic tool to an adjunctive tool to guide interventional management. This section will provide an overview of current multimodality imaging in the management of patients with VAs.

The classification of ventricular arrhythmia and the associated clinical outcome

心室心律不整的分類及相關之臨床預後

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Ventricular arrhythmias represent a clinical spectrum ranging from premature ventricular complexes (PVCs) to monomorphic ventricular tachycardia (VT) and polymorphic VT/ventricular fibrillation (VF). These arrhythmias can occur in the presence and absence of structural heart diseases (SHD). In patients with a structurally normal heart, ventricular arrhythmia can be subcategorized as idiopathic and those resulting from an inherited ion channel abnormality. Catheter ablation of ventricular arrhythmias has evolved considerably since first described >3 decades ago, especially in management of idiopathic VT and VT with SHD. The role of catheter ablation in inherited arrhythmias remains limited.

The Heart Rhythm Center of Taipei Veterans General have performed more than 1000 cases of VA ablation and more than 100 cases of epicardial ablation over the past decades. The clinical clues used to identify the need for an epicardial approach rely on the features of the VAs, disease entity, substrate characteristics of the endocardial mapping, and presence of intramural scarring in the imaging. In the past decade, the surface ECG of VAs has been used to provide initial information regarding the potential exit of the VT or extension of epicardial scarring. The need for and benefits of epicardial ablation have also been shown in certain diseases.

This lecture will focus on describing the techniques and outcomes of catheter ablation of idiopathic VT, and VT in patients with SHD.

The mechanism of ventricular electrical storm and neuromodulation

心室電風暴的神經調節和相關療法

Li-Wei Lo, Shih-Ann Chen

羅力瑋 陳適安

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Electrical storm is a severe state of ventricular electrical instability occurring in 4 to 20% (or even higher) of ICD patients, and it attacks in a non-random, temporal clustering fashion. Anti-adrenergic medication has been reported as one of the acute management during electrical storm, it means that autonomic status is an important factor that causing attacks of the storm.

Autonomic fluctuations play an integral role in the modulation of cardiac electrophysiology and its role in ventricular arrhythmogenesis is well recognized. The perturbation of autonomic nervous system may act on the vulnerable structural and electrophysiologic substrate and causing the initiation of the electrical storm. Sympathetic blockade, including sedation with intubation and ventilation, beta blocker have been applied as an acute therapy during attacks. Adjunctive intervention techniques, such as neuraxil modulation, including thoracic epidural anesthesia, stellate ganglion block and renal denervation have also been reported to improve the outcome. In this speech, we will summarize the mechanism of ventricular electrical storm and current advances in treating electrical storm by neuromodulation therapy.

Pharmacological management of electrical storm

心室電風暴藥物治療

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Electrical storm, defined as 3 or more separate episodes of ventricular tachycardia or ventricular fibrillation within 24 hours, carries significant morbidity and mortality. These unstable ventricular arrhythmias have been described with a variety of conditions including ischemic heart disease, structural heart disease, and genetic conditions.

The most common cause is ischemia, but evaluation of these patients at presentation should include assessment of other potential substrates and triggers such as worsening heart failure, medications, and genetic conditions. While implantable cardioverter-defibrillator implantation and ablation may be indicated and required, antiarrhythmic medication remains an important adjunctive therapy for these persons.

Initial treatment should include ACLS and stabilizing measures. Many patients with ES will require more definitive therapy, such as revascularization or ablation with an electrophysiology study, but application of optimal medical therapy remains an important adjunctive therapy. Use of β-blocker and amiodarone are cornerstones of therapy, but tailoring the treatment and antiarrhythmic therapy for the underlying condition and trigger is necessary.

Ablation and innovative management of electrical storm

心室性電風暴的電燒與創新治療

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The ventricular electrical storm is characterized by the clustering episodes of ventricular tachycardia/fibrillation (VT/VF) during a short period of time. The electrical storm occurs in 10-14% of patients with structural heart disease receiving an implantable cardioverter defibrillator (ICD) implantation. Undesirable cardioversion delivered by an ICD in patients with electrical storm can worsen the cardiac function and significantly increase the mortality. The clinical management of electrical storm frequently requires multidisciplinary approaches. In additional to the pharmacologic therapies, the correction of underlying problems (ie. ischemia, electrolyte imbalance, pro-arrhythmic medication), device reprogramming, mechanical hemodynamic support, intubation with deep sedation, and neuraxial modulation (ie. thoracic epidural anesthesia, cardiac sympathetic denervation), radiofrequency catheter ablation has been implemented to restore stable sinus rhythm. The application of radiofrequency catheter ablation should be considered within 48 hours after hospitalization, especially for those receiving multiple shocks or ICD interventions after the appropriate management. The achievement of complete elimination of VT and negative inducibility is also associated with lower VT recurrences during long-term follow-up. It has also been proved to be beneficial regarding VT recurrences in both low- and high-risk patients.

Furthermore, in spite of the advancement of ablation strategy, clinical hurdle persisted in those with unstable VT/VF, unmappable ventricular tachyarrhythmias and/or unable/failed ablation owing to the anatomic consideration, substrate characteristics and radiofrequency energy penetration. Recent case series have proved the safety and efficacy of radiation therapy as an alternative and noninvasive strategy for the above patients based on the image-derived scar distribution and noninvasive localization of ventricular arrhythmias. Future study will be appreciated to validate the role of radiotherapy in patients with VT/VF storm.

The ICD troubleshooting in ventricular electrical storm

心室性電風暴心臟去顫器的故障排除

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ICD Troubleshooting

Implantable cardioverter defibrillators have become the treatment of choice for primary and secondary prevention of sudden cardiac death and has been demonstrated to be the superior treatment for patients at risk for life-threatening ventricular arrhythmias. Clinically, ICD therapy may be associated with a variety of problems including lead dislodgement or fracture, device malfunction, and inappropriate therapy. Sensing problems provide major challenges for ICDs therapy. These include under-sensing of VF, atrial under-sensing, and oversensing in relation to SVT–VT discrimination, and unique issues related to sensing subcutaneous electrograms. Unnecessary implanted cardioverter defibrillator (ICD) shocks can be reduced by proper programming of detection rate and duration, anti-tachycardia pacing, and algorithms that discriminate supraventricular tachycardia from ventricular tachy- cardia. Clinician should have a thorough understanding of the underlying physics and signal processing techniques.

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家庭醫學與基層醫療之病人自述健康成效研究

Patient Reported Outcome Research in Primary Care

協辦單位：臺北榮總家庭醫學部

時 間：108年6月22日 13:30~17:20

Time：June 22, 2019 13:30~17:20

地 點：台北國際會議中心 三樓 北軒會議室

Place：3 Floor, Conference Room North Lounge
Taipei International Convention Center

家庭醫學與基層醫療之病人自述健康成效研究

Patient Reported Outcome Research in Primary Care

Patient reported outcome research in primary care

家庭醫學與基層醫療之病人自述健康成效研究

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The ultimate goal of health care is to restore or improve health, and health is the means to well-being. The person is the best judge of his/her own well-being. Patient reported outcome (PRO), defined as an outcome reported by the patient based on his/her own perception, is a construct to capture the person's subjective perception. Symptoms are the most classic example of a patient reported outcome that has long been recognized as the most important clinical information in the diagnosis and evaluation of management outcome. PRO research has developed rapidly in the last 50 years since the health outcome movement in the 1960s, especially in the conceptualization and operationalization of health-related quality of life (HRQOL) measures. The availability of valid, reliable and standardized HRQOL measures has enabled PRO used as a scientific outcome measure. PRO is highly relevant to research in primary care that emphasizes person-centered care, whole-person care and function. This presentation will illustrate with examples of PRO research in primary that have produce important evidence to support health policy, clinical practice and future research. HRQOL is more sensitive than traditional clinical outcomes in measuring the social inequity of health, the quality of care of different primary care providers, impact of illnesses, the effectiveness of alternative interventions, and health service needs. The next challenge in PRO research in primary care is on how HROQL can be implemented in routine clinical practice.

Integration of quality of life and survival for evaluation of healthcare technology: Methods and empirical examples

整合生活品質與存活函數作醫療科技評估：方法與實例

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Survival and quality of life (QOL) are two key measurements for outcome evaluation in health care services. Integrating these two outcome functions together can derive an equation in universal healthcare evaluation with quality-adjusted life year (QALY) as the common unit, when the QOL is measured in utility or preference value. Because many patient cohorts are only followed for a limited period of time with a high censored rate or above 50%, we have developed a semi-parametric method that borrows information from age-, sex-, and calendar-year matched general population for extrapolation of survival function to life time. By subtracting the life expectancy and/or quality-adjusted life expectancy (QALE) from the corresponding age-, sex- and calendar-year matched referents, we are able to estimate the expected years of life loss (EYLL) and loss of QALE for a specific illness, which would be the expected health benefit from the healthcare technology after adjustment of different age and sex distribution and lead time bias. When the QOL function is replaced by medical cost reimbursed by the National Health Insurance (NHI), we can obtain the lifetime financial burden for a specific health condition. Then, we shall be able to quantify the cost-per-life year and/or cost-per-QALY saved for the specific technology, which are useful to improve the efficiency, equity and sustainability of NHI. Empirical examples of cancer, dialysis, stroke, head injury, and prolonged mechanical ventilation are provided as a demonstration of feasibility and usefulness in health technology assessment.

Study design and statistical analysis in patient reported outcome research

病人自述健康成效研究之研究設計與統計分析

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Patient-reported outcomes (PRO) research has been a hot-spot topic for years, not just in clinical research but also in all fields of health care. The validity and reliability of their measurement tools are the critical issues. So, the confirmation mechanism is always provided and hidden in the study design. This talk illustrates our Shihpai cohort for cardiovascular metabolic risk factors and outcome study in Taipei Veterans General Hospital as a good PRO research practice.

The Shipai area is situated in two districts, Beitou and Shilin, approximately one-half the size of Taipei City, and has about one-fifth the population size. We conducted a pilot community-based cohort in 2010. Residents were randomly sampled by age (young adults: 35–44 years and middle-aged adults: 45–55 years) and urbanization. Participants were scheduled to receive examinations (physical and blood) and answer questionnaires. A ten-year follow-up is anticipated. Metabolic syndrome (MetS) was defined based on the Adult Treatment Panel III guidelines. Health-related quality of life (HRQoL) were assessed by the Short Form Health Survey (SF-36), Taiwan version.

After screening, 906 participants were enrolled. The preliminary result showed that MetS was diagnosed in 17.9% (men 25.4% and women 13.2%). Central obesity (odds ratio 23.7) was being the most urgent preventive focus. After adjustment, women but not men with more components of MetS had significantly lower physical component summary (PCS) scores. The gender differences was shown in the association between MetS and HRQoL among middle-aged adults in Taiwan. After two years follow-up, the progression rate of participants with no MetS component was 37.2%, while the recovery rate of those with only one MetS component was 27.7%.

In the long run, our Shipai cohort research can provide a well cohesiveness with the community, and mutually supportive to achieve the goal of preventive medicine and healthy aging.

Patient reported outcome research in the community: The Yilan study

病人自述健康成效之社區研究：健康活樂宜蘭市計畫

Nai-Wei Hsu

徐迺維

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宜蘭縣政府衛生局 及 國立陽明大學

In recent years, there has been an increased focus on the patient reported outcome research with different validated measures, such as the health-related quality of life (HRQoL). One of the goals is trying to improve the quality, safety and clinical effectiveness of the health care provided to the people. However, there are still some problems requiring further evaluations. One of them is whether various factors have different impacts on the patient reported outcome. Another is whether the patient reported outcomes, such as the HRQoL, really reflect the true physical and mental status of the people.

Since 2012, the Community Medicine Research Center of the National Yang-Ming University and the Center of the Community Medicine of the National Yang-Ming University Hospital have implemented a community-based prospective cohort study, which used health survey questionnaire (including the Short Form-12 Health Survey) and physical examination to assess both the physical and mental conditions of all the people aged 65 years and above dwelling in the Yilan City, one of the most populated city in Yilan County. The first survey has been completed from 2012 to 2017. Totally there were 11,268 aged residents been invited and 3,982 of them participated and completed the questionnaires. The mean age of the participants was 76.1 ± 6.7 years and 57% of the them were female.

One of our researches disclosed that various factors, including mental function, some chronic diseases (such as cardiovascular disease and stroke), and age have different impacts on the HRQoL. Besides, anxiety and depression could mediate the effects of cardiovascular disease and stroke on the HRQoL. In another research about the association between the body mass index and the patient reported outcomes, we found that as compared to normal-weight individuals, overweight individuals had better mental HRQoL and similar physical HRQoL, which has been different from what we have believed before. Further studies will be necessary to expand our knowledge of those factors having different implications on the patient reported outcomes and the associations between these outcomes and the real healthy status of the people.

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脊椎研討會

Spine International Seminar and Clinical Case Discussion

時 間：108年6月22日 08:30~11:30

Time：June 22, 2019 08:30~11:30

地 點：台北國際會議中心 三樓 北軒會議室

Place：3 Floor, Conference Room North Lounge
Taipei International Convention Center

脊椎研討會

Spine International Seminar and Clinical Case Discussion

「醫學研究論文獎」及
「盧致德獎」論文摘要

「盧致德獎」
(從刊登於中華醫學會雜誌上的全部論文中，選出被引用
20 次以上的作者，並以其中最多次者頒發盧致德獎)

「醫學研究論文獎」及「盧致德獎」論文摘要

1. 財團法人中華醫學研究獎助基金會
   Mesenchymal stem cells and their conditioned medium can enhance the repair of uterine defects in a rat model ..... 臺北榮總 婦女醫學部 何積泓醫師

2. 財團法人消化醫學研究發展基金會
   The effects of proton pump inhibitor on hepatic vascular responsiveness and hemodynamics in cirrhotic rats ..... 臺北榮總 胃腸科 辛怡芳醫師

3. 財團法人兼善醫學基金會
   Generation of high quality of hepatocyte-like cells from induced pluripotent stem cells with Parp1 but lacking c-Myc ..... 振興醫院 大腸直腸外科 黃啟栓醫師

4. 財團法人心臟醫學研究發展基金會
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Mesenchymal stem cells and their conditioned medium can enhance the repair of uterine defects in a rat model

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Abstract

Background. Our aim was to examine the roles of mesenchymal stem cell (MSC) transplantation in the repair of large uterine defects.

Methods. Uterine defects were created in both uterine horns of female rats by a punch instrument, and bone marrow-derived MSCs, MSC-conditioned medium (MSC-CM) or vehicle were injected into the myometrium around the defect. The rate of uterine defect repair was monitored on day 2 and 4 after operation. Cytokine array of MSC-CM was performed, followed by neutralizing antibody experiments to clarify the exact cytokine participating in the MSC-CM-enhanced wound repair.

Results. Transplantation of MSCs, but not myometrial cells, significantly enhanced uterine defect repair. The transplanted MSCs were detected in the uterine horn with no signs of rejection on day 4 after transplantation, when the MSC-transplanted uterine wound was nearly healed. Moreover, uterine defect repair was also accelerated by injection of MSC-CM, indicating the paracrine effects of MSCs on uterine wound healing. Cytokine array analysis further revealed that MSC-CM contained abundant cytokines and chemokines, among which high levels of interleukin-6 (IL-6) were found. Additionally, antibodies against IL-6 were shown to block MSC-CM-enhanced uterine defect repair.

Conclusion. This study demonstrated that transplantation of MSCs could enhance uterine defect repair by paracrine effects involving IL-6, which are findings that may be applied to facilitate uterine wound healing in the removal of huge intramural masses.

Keywords. Mesenchymal stem cells; Paracrine effects; Transplantation; Uterine defect repair; Uterine surgery

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The effects of proton pump inhibitor on hepatic vascular responsiveness and hemodynamics in cirrhotic rats

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Abstract

Background. Liver cirrhosis is associated with increased intrahepatic resistance due to hepatic fibrosis and exaggerated vasoconstriction. Recent studies have indicated that proton pump inhibitors (PPIs), in addition to acid suppression, modulate vasoactive substances and vasoresponsiveness. PPIs are frequently prescribed in patients with cirrhosis due to a higher prevalence of peptic ulcers, however other impacts are unknown.

Methods. Liver cirrhosis was induced in Sprague-Dawley rats with common bile duct ligation (BDL). On the 29th day after BDL and after hemodynamic measurements, the intrahepatic vascular responsiveness to high concentrations of endothelin-1 (ET-1) was evaluated after preincubation with (1) Krebs solution (vehicle), (2) esomeprazole (30 μM), or (3) esomeprazole plus N^{ω}-nitro L-arginine (NNA, a non-selective NO synthase (NOS) inhibitor, 10^{-4} M). After perfusion, the hepatic protein expressions of endothelial NOS (eNOS), inducible NOS (iNOS), cyclooxygenase (COX)-1, COX-2, endothelin-1, DDAH-1 (dimethylarginine dimethylaminohydrolase-1, ADMA inhibitor), DDAH-2, ADMA (asymmetrical dimethyl arginine, NOS inhibitor) were evaluated. In the chronic model, the BDL rats received (1) vehicle; or (2) esomeprazole (3.6 mg/kg/day, oral gavage) from the 1st to 28th day after BDL. On the 29th day and after hemodynamic measurements, plasma liver biochemistry and liver fibrosis were evaluated.

Results. Esomeprazole did not affect hepatic ET-1 vasoresponsiveness. The hepatic protein expressions of the aforementioned factors were not significantly different among the groups. There were no significant differences in hemodynamics, liver biochemistry and hepatic fibrosis after chronic esomeprazole administration.

Conclusion. PPIs did not affect hepatic vasoresponsiveness or the release of vasoactive substances. Furthermore, they did not influence hemodynamics, liver biochemistry or severity of hepatic fibrosis in the cirrhotic rats.

Keywords. Endothelin; Liver cirrhosis; Nitric oxide; Portal hypertension; Proton pump inhibitor

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Generation of high quality of hepatocyte-like cells from induced pluripotent stem cells with Parp1 but lacking c-Myc

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Abstract

Background. Induced pluripotent stem cells (iPSCs) have a great potential for application in patient-specific therapy. The reprogramming method that does not involve c-Myc reduces tumorigenic risk, but also largely reduces the efficiency of generation of iPSCs, especially for those reprogrammed from damaged cells. Poly(ADP-ribose) polymerase 1 (Parp1) catalyzes a reaction of poly(ADP-ribosylation) and has been reported to enhance cell reprogramming.

Methods. Using Oct-4/Sox2/Klf4/Parp1 (OSKP) reprogramming method, reprogramming factors plus Parp1 were capable of generation of iPSCs from adult fibroblasts and further toward to differentiate from iPSCs status into hepatocyte-like cells.

Results. Our results showed that Oct-4/Sox2/Klf4/Parp1 (OSKP)-derived iPSC exhibited regular pluripotent properties, long-term passages and more stable cellular-divided period. These OSKP-derived iPSCs can effectively differentiate into hepatocyte-like cells (OSKP-iPSC-Heps), and present high mRNA levels of Sox17, HNF3b, and HNF4a in OSKP-iPSC-Heps. The mature hepatic functions, including CYP3A4, LDL uptake, glycogen synthesis and urea secretion were analyzed and well detected in OSKP-iPSC-Heps on day 14 post-differentiation.

Conclusion. In conclusion, we demonstrated that Parp1 promoted reprogramming process to generate the high quality of iPSCs, which could be used as a high quality source of hepatocytes.

Keywords. Hepatocyte; Induced pluripotent stem cells; Poly(ADP-ribose) polymerase 1

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Anti-atherosclerotic effect of Fermentum Rubrum and *Gynostemma pentaphyllum* mixture in high-fat emulsion- and vitamin D_3-induced atherosclerotic rats

San-Hu Gou [a], Bei-Jun Liu [a], Xiu-Feng Han [b], Li Wang [b], Chao Zhong [b], Shan Liang [b], Hui Liu [b], Yin Qiang [b], Yun Zhang [b], Jing-Man Ni [a,b,*]

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Abstract

Background. The mixture of Hongqu and gypenosides (HG) is composed of Fermentum Rubrum (Hongqu, in Chinese) and total saponins of *Gynostemma pentaphyllum* (Thunb.) Makino (Jiaogulan, in Chinese) in a 3.6:1 weight ratio. Both Hongqu and Jiaogulan are considered valuable traditional Chinese medicines (TCMs); they have been commonly used in China for the treatment of hyperlipidemia and related diseases for centuries. The aim of the current study was assess the anti-atherosclerotic effect of HG.

Methods. Sixty-four Wistar rats were randomly divided into eight groups: normal, model, positive control (simvastatin, 1 mg/kg), Hongqu-treated (72 mg/kg), gypenoside (total saponin)-treated (20 mg/kg), and three doses HG-treated (50, 100, and 200 mg/kg). All of the rats were fed a basal diet. Additionally, the model group rats were intragastrically administered a high-fat emulsion and intraperitoneally injected with vitamin D_3. The serum lipid profiles, oxidative stress, inflammatory cytokine, and hepatic antioxidant levels were then determined. Furthermore, the liver histopathology and arterial tissue were analyzed, and the expression of hyperlipidemia- and atherosclerosis (AS)-related genes was measured using reverse transcription-polymerase chain reaction.

Results. The AS rat model was established after 80 days. Compared to the model group, the HG-treated groups showed an obvious improvement in the serum lipid profiles, oxidative stress, and inflammatory cytokine levels, and showed markedly increased hepatic total antioxidant capacity. Moreover, the expression of genes related to lipid synthesis and inflammation reduced and that of the genes related to lipid oxidation increased in the liver and arterial tissue, which also reflected an improved health condition.

Conclusion. the anti-atherosclerotic effects of HG were superior to those of simvastatin, Hongqu, and the gypenosides. Therefore, HG may be a useful anti-atherosclerotic TCM preparation.

Keywords. Atherosclerosis; Fermentum Rubrum; *Gynostemma pentaphyllum*; Gypenosides; Hyperlipidemia; Red yeast rice

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Distinguishing non-obstructive azoospermia from obstructive azoospermia in Taiwanese patients by hormone profile and testis size

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Abstract

Background. An accurate diagnosis of the etiology of azoospermia is crucial, as sperm retrieval methods differ between patients with non-obstructive azoospermia (NOA) and obstructive azoospermia (OA). The aim of this study was to determine hormone and testes size cutoff values to identify the cause of azoospermia in Taiwanese patients.

Methods. The medical records of azoospermic patients were retrospectively collected from April 2008 to July 2016, including hormone profile, physical examination findings, and testes size. Bilateral testes biopsies or microdissection testicular sperm extraction were performed in all patients for a definite diagnosis. The diagnostic parameters used to distinguish NOA from OA were analyzed using the *t*-test and receiver operating characteristic curves.

Results. A total of 51 patients with OA and 156 with NOA were included. The mean levels of testosterone (4.5 vs. 3.4 ng/ml) and E2 (26.3 vs. 19.2 pg/ml) were significantly higher in the OA group, whereas the levels of follicular stimulating hormone (FSH) (5.6 vs. 25.4 mIU/ml) and Leutinizing hormone (LH) (3.7 vs. 11.6 mIU/ml) were lower. Receiver operating characteristic curve analysis revealed that FSH and right testis size were the best individual diagnostic predictors. Using a combination of FSH > 9.2 mIU/ml and right testis size < 15 ml, the positive predictive value for NOA was 99.2% and 81.8% for OA.

Conclusion. A combination of FSH > 9.2 mIU/ml and right testis size < 15 ml was a strong predictor of NOA in our Taiwanese patients.

Keywords. Azoospermia; FSH; Hormone; Testis

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Warfarin accelerated vascular calcification and worsened cardiac dysfunction in remnant kidney mice

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Abstract

Background. Vascular calcification is highly prevalent in end-stage renal disease (ESRD) and is a significant risk factor for future cardiovascular events and death. Warfarin use results in dysfunction of matrix Gla protein, an inhibitor of vascular calcification. However, the effect of warfarin on vascular calcification in patients with ESRD is still not well characterized. Thus we investigated whether arterial calcification can be accelerated by warfarin treatment both *in vitro* and *in vivo* using a mouse remnant kidney model.

Methods. Human aortic smooth muscle cells (HASMC) were cultured in medium supplemented with warfarin and phosphate to investigate the potential role of this drug in osteoblast transdifferentiation. For *in vivo* study, adult male C57BL/6 mice underwent 5/6 nephrectomy were treated with active vitamin D3 plus warfarin to determine the extent of vascular calcification and parameters of cardiovascular function.

Results. We found that the expressions of Runx2 and osteocalcin in HASMC were markedly enhanced in the culture medium containing warfarin and high phosphate concentration. Warfarin induced calcification of cultured HASMC in the presence of high phosphate levels, and this effect is inhibited by vitamin K2. Severe aortic calcification and reduced left ventricular ejection fractions were also noted in 5/6 nephrectomy mice treated with warfarin and active vitamin D3.

Conclusion. Warfarin treatment contributes to the accelerated vascular calcification in animal models of advanced chronic kidney disease. Clinicians should therefore be aware of the profound risk of warfarin use on vascular calcification and cardiac dysfunction in patients with ESRD and atrial fibrillation.

Keywords. Left ventricular dysfunction; Uremia; Vascular calcification; Warfarin

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Evaluating cerebral hemodynamics using quantitative digital subtraction angiography and flat-detector computed tomography perfusion imaging: A comparative study in patients with carotid stenosis

Liang-Wei Chen [a], Chung-Jung Lin [a,b], Wan-Yuo Guo [a,b,*], Sheng-Che Hung [a,b], Han-Jui Lee [a,b], Ko-Kung Chen [c], Feng-Chi Chang [a,b], Chao-Bao Luo [a,b], Wei-Fa Chu [a,b]

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Abstract

Background. The efficacy of both quantitative digital subtraction angiography (QDSA) and flat-detector computed tomography perfusion (FD-CTP) is equivalent to that of magnetic resonance perfusion (MRP) in assessing perfusion deficits in carotid stenosis. This study evaluated the feasibility of using FD-CTP to monitor cerebral hemodynamics during carotid stenting.

Methods. Thirteen patients with extracranial carotid stenosis (>70%) were included. Both QDSA and two FD-CTP sessions were performed before and after carotid stenting. Cerebral circulation time (CCT) was defined as the difference between the time to peak (TTP) of the parietal vein and the cavernous internal carotid artery. For FD-CTP and MRP, regions of interest (ROIs) were placed in the middle cerebral artery territory at the basal ganglia level of both stenotic and contralateral hemispheres for measurement. The TTP ratio (rTTP) was defined as stenotic TTP divided by contralateral TTP; and ratio of cerebral blood volume (rCBV), ratio of mean transit time (rMTT), and ratio of cerebral blood flow (rCBF) were defined similarly. Both CCT and ratio perfusion parameters were compared during stenting.

Results. Before stenting, only rCBF ($r = 0.73$) and rTTP ($r = 0.58$) demonstrated correlations between FD-CTP and MRP; CCT correlated with only rMTT in MRP ($r = 0.69$). After stenting, only rCBF ($r = 0.56$) indicated a correlation between FD-CTP and MRP. Regarding cerebral flow after stenting, CCT (4.61 ± 1.6 s) was shortened, rMTT (1.12 ± 0.04) and rTTP ($r = 1.05 \pm 0.03$) decreased, and rCBF (0.91 ± 0.16) increased significantly.

Conclusion. FD-CTP provides a potentially more comprehensive hemodynamic assessment of parenchymal perfusion changes compared with QDSA during carotid stenting, but FC-CTP requires additional 18 min. FD-CTP confirmed that the normalization of cerebral hemodynamics began immediately and continued for 1—3 days.

Keywords. Carotid stenosis; Carotid stenting; Cerebral circulation time; Cerebral hemodynamic; Flat-detector; Perfusion; Quantitative digital subtraction angiography

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The clinical impact of the novel tumor marker DR-70 in unresectable gastric cancer patients

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Abstract

Background. Gastric cancer tumor markers, such as carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9), have been applied in clinical practice to screen or monitor treatment responses. However, their sensitivity and specificity are unsatisfactory. Therefore, we assessed the novel tumor marker DR-70 and evaluated its performance in screening and response monitoring.

Methods. The study included newly diagnosed patients with advanced gastric cancer from March 2012 to October 2015. We measured the DR-70, CEA, and CA 19-9 levels at the time of enrollment. The patients subsequently underwent chemotherapy. We followed-up the patients every 3 months; DR-70 levels and abdominal computed tomography scans were re-evaluated and repeated, respectively, at each follow-up. The correlation between treatment response and DR-70 level after chemotherapy was analyzed. The overall survival and progression-free survival rates were also evaluated.

Results. A total of 51 patients with gastric cancer were enrolled. Most (82.4%) had metastatic disease. At enrollment, the sensitivity of DR-70 in our study group was 78.4%, compared with 52.9% and 43.1% for CEA and CA 19-9, respectively. When we used the three tumor markers together, the sensitivity increased to 80.4%. We observed a correlation between treatment response and DR-70 level after chemotherapy. No difference in either overall survival or progression-free survival was observed between the DR-70 positive and negative groups. However, a trend toward poorer overall survival was observed for the high DR-70 group, although this was not statistically significant.

Conclusion. DR-70 is a powerful tool not only for screening unresectable gastric cancer but also for treatment response evaluation.

Keywords. Chemotherapy; Gastric cancer; Prognosis; Tumor markers

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Chromobacterium violaceum infection: A clinical review of an important but neglected infection

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Abstract

Background. Increasing reported cases with *Chrombacterium violaceum* infection has been noticed in recent decades. It is noteworthy for its difficult-to-treat entity characterized by a high frequency of sepsis, easily distantant metastasis, multidrug-resistance, and frequent relapse, and high mortality rate.

Methods. The English-language literature was reviewed from 1952 through December 2009 by an electronic view via the PubMed and Medline databases and manual searches.

Results. One hundred and six patients with *Chrombacterium violaceum* infection from the literature were studied. The four leading clinical manifestations reviewed in the published literature, in the order of frequency, were fever (100%), sepsis (82%), skin lesions (67.9%), and abdominal pain (31.1%). Localized abscess was found in 52 patients (49%) and liver was the mostly common involved organ. Fifty-six patients (53%) were dead. Almost all of the penicillin, ampicillin, and first and second-generation cephalosporins exhibited totally resistant to *Chrombacterium violaceum*. The most important risk factors in mortality in 61 patients with *Chrombacterium violaceum* bacteremia were at a young age (p = 0.0789), presence of localized abscess (p = 0.030), shorter clinical course ($p < 0.001$), and inappropriate antimicrobial treatment ($p < 0.001$). Seven patients (6.6%) experienced of relapse or reinfection, with a median interval of 135 days (range, 4 to 1095 days).

Conclusions. A high index of suspicion for *Chromobacterium violaceum* infection is required along with prompt diagnosis, optimal antimicrobial therapy, and adequate therapeutic duration for a successful therapy.

Keywords. Abscess; *Chromobacterium violaceum* infection; Difficult-to-treat; Metastasis; Multidrug-resistant; Relapse

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- Synthetic Aprotinin 作為抗纖維蛋白溶解劑，預防纖維蛋白凝塊過早分解

Reference :

1. Sierra DH. Fibrin sealant adhesive systems: a review of their chemistry, material properties and clinical applications. *J. Biomater Appl.*

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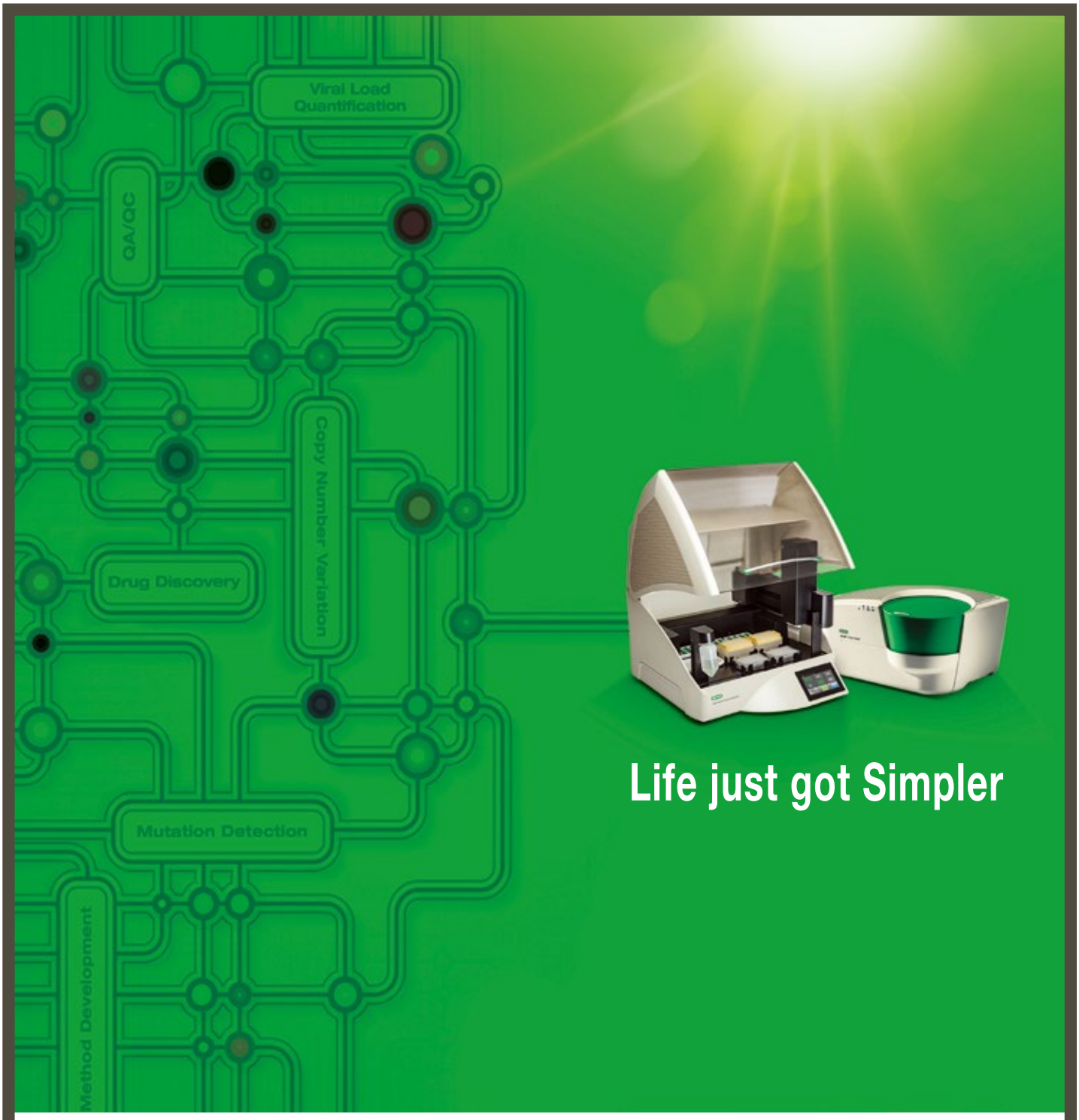
TWN/90/16-0006



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健保給付年齡已放寬[1]

NEW!

年齡大於等於五十歲之骨關節炎患者

≥ 50 歲*

之

OA† 患者

即可健保給付 CELEBREX®

*Celecoxib 可用於年齡大於等於五十歲之骨關節炎病患　†骨關節炎 (Osteoarthritis, OA)

CELEBREX® 骨關節炎用法用量[2]：

用法用量/建議劑量，應依個別病人的治療目標使用最低有效劑量

Reference: 1.CELEBREX 藥品給付規範 2.CELEBREX 中文仿單 USPI 201806-3

北衛藥廣字第 10801014 號

【處方說明】CELEBREX® 簡易處方資訊 USPI 201806-3

【成分】CELEBREX® 口服膠囊劑的規格有 Celecoxib 200 毫克 **【適應症】**緩解骨關節炎之症狀與徵兆，緩解成人類風濕性關節炎之症狀與徵兆，緩解成人急性疼痛及治療原發性經痛，緩解僵直性脊椎炎之症狀與徵兆。**【用法用量】**骨關節炎解除骨關節炎徵象及症狀的建議劑量為每天 200 mg，單次服用；或以每天二次、每次 100 mg 的方式給藥亦可。類風濕性關節炎：解除類風濕性關節炎徵象及症狀的建議劑量為每天二次、每次 100 至 200 mg。僵直性脊椎炎 (AS)：為治療僵直性脊椎炎的徵象及症狀，CELEBREX® 的建議劑量為每天 200 mg，單次 (每天一次) 或分次 (每天二次) 給藥。六週後若未見效，可嘗試每天 400 mg 之劑量，6 週後若仍未見效，就不會有療效反應，應考慮改用別的治療。緩解急性疼痛及治療原發性痛經：第一天之建議起始劑量為 400 mg，需要時可再服用 200 mg。接下來的建議劑量為需要時每天二次，每次 200 mg。特殊族群：中度肝功能損傷病人 (Child-Pugh 分級 B 級) CELEBREX® 的每日建議劑量必須降低 50%。對於嚴重肝功能損傷病人，不建議使用 CELEBREX®。CELEBREX® 不建議用於併有嚴重腎功能損傷的病人。**【禁忌症】**已知對 Celecoxib、aspirin 或其它 NSAIDs、藥品中任何成份過敏的病人。曾對磺醯胺 (sulfonamides) 產生過敏反應的病人。曾於服用 aspirin 或其它 NSAIDs 之後出現氣喘、蕁麻疹、或其他過敏反應的病人。此類病人曾有對 NSAIDs 產生嚴重、有時致死的全身性過敏反應的報告。進行冠狀動脈繞道手術 (CABG) 之後 14 天內禁用本藥。**【警語和注意事項】**心血管血栓栓塞事件：NSAIDs 藥品會增加發生嚴重心血管栓塞事件之風險，包括心肌梗塞和中風，且可能為致命的。此風險可能發生在使用該類藥品的初期，且使用藥品的時間越長，風險越大。高血壓：NSAIDs (包括 CELEBREX®) 可能導致新的高血壓發病或使原有的高血壓惡化，進而促使心血管事件的發生率增加。使用血管收縮素轉化酶(ACE)抑制劑、thiazides 或環利尿劑的病人，服用 NSAIDs 期間，對這些療法的反應可能會減弱。胃腸道 (GI) 出血、潰瘍及穿孔：NSAIDs 導致增加嚴重胃腸道 (GI) 不良事件危險包括可引發致死性的腸道的出血、潰瘍及穿孔。這些事件可發生在治療期任何時間而且沒有警示症狀。老年人及先前有消化性潰瘍病史或胃腸道 (GI) 出血的病人有較高的危險會出現嚴重事件。**【不良反應】**頭痛、消化不良、上呼吸道感染、腹瀉、竇炎、腹痛等。

詳細處方資訊請參考完整仿單

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FAX:(07)535-7676

CELEBREX® CELECOXIB 200MG CAPSULE 希樂葆®

PP-CEL-TWN-0178-201901

ONE Plavix®

改善腦、心、周邊栓塞疾病

有效降低中風、急性冠心症、與周邊動脈栓塞的發生，值得醫師信賴

ACS: acute coronary syndrome
PAD: peripheral artery disease

[處方資訊摘要] (詳細內容請參照衛生福利部核准之完整產品說明書內容)
仿單版本Plavix 75mg_LPI_C_CCDS v23

Plavix® 75mg 處方資訊 每錠含Clopidogrel hydrogen sulphate 97.875mg（相當於Clopidogrel 75mg）衛署藥輸字第 022932 號

【適應症】• 降低近期發生中風、心肌梗塞或周邊動脈血管疾病的粥狀動脈硬化病人之粥狀動脈栓塞事件（如：心肌梗塞、中風或其他因血管病變引起的死亡）的發生。 • 與aspirin併用降低非ST段上升之 急性冠心症（不穩定性心絞痛和非0波型心肌梗塞）病人（包括經皮冠狀動脈介入性治療後放置支架的患者）之粥狀動脈栓塞事件" • 與aspirin併用可用於以內科治療的ST段上升之急性心肌梗塞病人中•不適合接受Vitamin K antagonists的心房纖維顫動患者，併有至少一個發生血管事件危險因子，且屬於出血危險性低者，可與aspirin併用以預防粥狀動脈栓塞及血栓栓塞事件，包括中風。**【劑量和用法】** 成年和老年人：Clopidogtel的建議劑量為每天75mg，一天一次，可和食物同時服用或分開服用。**【禁忌】**• 對藥品主成份或其他非活性成份過敏者。 • 嚴重肝功能不良的患者。 • 正在出血的患者如消化 性潰瘍或顱內出血的患者。 • 懷孕及授乳婦**【警語及注意事項】**由於有血液學方面的不良反應和出血的危險，在治療期間應檢驗血球計數，且當出現有出血的臨床症狀時應立即進行適當的檢查（請參考"不良反應欄"）和其他抗血小板製劑一樣，dopidogrel應小心使用於可能有出血危險的病人，例如：創傷、手術、其他病理狀況或接受aspirin、肝素、glycoprotein IIb/IIIa抑制劑或非固醇類抗炎止痛劑（NSAID）包括Cox-2抑制劑或選擇性血清素商吸收抑制劑(SSRIs)。病人應小心注意任何可能的出血徵兆，包括隱匿性的出血，特別是在治療開始的第一週及手術或侵入性心臟檢查後。由於可能會增加出 血的危險，clopidogrel不建議與口服抗凝血劑併用**【交互作用】**口服抗凝血劑：由於可能增加出血的危險，不建議clopidogrel與warfarin併用。選擇性血清素再吸收抑制劑(SSRIs)：由於SSRIs會影響血小板活動及增加出血的風險，併用SSRIs和clopidogrel時應小心。**【懷孕】**由於資料不足，懷孕期間不建議使用Clopidogrel。**【授乳】**目前未知clopidogrel是否會經由人類的乳汁排泄。動物試驗顯示clopidogrel會分泌於乳汁中。為謹慎起見接受Planix治療時應停止授乳。**【副作用】**已有超過44,000位參加臨床試驗的病人使用clopidogrel來評估其安全性，包括治療超過一年以上的12,000位病人。整體而言，在 CARPIE試驗中clopidogrel 75 mg/day與aspirin 325 mg/day所出現與臨床相關的不良反應相當且不受年齡、性別和種族的影響。在CAPRIE、CURE、CLARITY、COMMIT及ACTiVE-A試驗中所出現的與臨床相關之不良反應如下。除臨床試驗經驗之外，亦包含自發性不良反應通報。出血是最常被報告的上市後不良反應，大部分的回報病例均發生在用藥的第一個月內。**【過量】**服用過量的clopidogrel會導致出血時間延長及其他出血的併發症。若發生出血應採取適當之治療，目前並未發現ciopidogrel的解毒劑，若需要立即校正過長的出血時間，輸血小板可能可以校正ciopidogrel的作用**【藥理特性】** ATC Code: B01 AC/040。

北市衛藥廣字第108010389號

使用前詳閱說明書
警語及注意事項

SANOFI

SATW.CLO.18.12.0438

SOLIQUA™
insulin glargine (100 U/mL) & lixisenatide

衛福部食藥署核准
Basal + GLP-1 RA
複方針劑注射筆

空腹血糖 + 餐後血糖
合併治療 機轉互補

併用治療可達到較大的HbA1c降幅，不易增加低血糖的發生率

Soliqua™ 內含作用機轉互補的兩種活性成分

Insulin Glargine主要針對空腹血糖
Lixisenatide 主要針對餐後血糖，會延緩胃排空，降低餐後葡萄糖的吸收速率

爽胰達注射劑100單位+50微克
Soliqua solution for injection 100 units +50 μg

衛部菌疫輸字第001080號
本藥限由醫師使用

1. 藥品名稱
爽胰達注射劑100 units /mL + 50 μg/mL之預填注射筆

2. 組成
Soliqua 100 units/mL + 50 μg /mL 注射劑之預填注射筆
每支預填注射筆3 mL溶液內含有insulin glargine*300 units及lixisenatide 150 μg。每 mL含有insulin glargine 100 units及lixisenatide 50 μg。每個劑量步驟含有insulin glargine 1 units及lixisenatide 0.5 μg。

3. 適應症
Soliqua適於基礎胰島素(每日劑量少於60單位)或lixisenatide治療時血糖控制不佳的第二型糖尿病成人病人，在飲食與運動外，做為改善血糖之輔助治療。

4. 劑量
劑量係依照個人的臨床反應及病人對胰島素的需求作調整。Lixisenatide的劑量會隨著insulin glargine的劑量而有所增加或減少且視所使用的注射筆而定。
Soliqua應於餐前一小時注射，每日一次。當選定最方便注射的那一餐後，最好每日都固定在同一餐前進行注射。
起始劑量： Soliqua開始給藥前應先停用基礎胰島素或lixisenatide。Soliqua的起始劑量乃依先前的抗糖尿病治療而定，且lixisenatide的起始建議劑量不得超過10 μg

		lixisenatide	Insulin glargine (100 units/ml)**
			≥20 ~ <30 units
起始劑量及注射筆	Soliqua (10~40) 注射筆	10 個劑量步驟(10 units/5 μg)*	20 個劑量步驟 (20 units/10 μg)*

若使用不同的基礎胰島素
若基礎胰島素為每日給藥2次或使用insulin glargine (300 units/mL)，則先前給藥的每日總劑量應下調20%以作為Soliqua 起始劑量(20 units/10μg或30 units/10μg)的選擇依據。任何其他基礎胰島素的計算方式與insulin glargine (100 units/mL)相同。
劑量調整： Soliqua的劑量應依照個別病人對胰島素的需求給藥，建議依據空腹血糖值調整劑量以使血糖獲得最佳控制，建議在藥物更換期間及隨後幾週對血糖進行嚴密監測。
- 若病人以Soliqua (10 40)注射筆開始使用，追支筆的最高劑量可調整至40個劑量步驟。
- 病人只有在適當監測血糖的醫療監督下才能調整用筆劑量或給藥時間 。
- 特殊族群如老年人(≥65歲)、腎功能不全、肝功能不全及兒童等資訊，請詳見仿單。

5. 禁忌
對活性成分或任何賦形劑甘油、甲硫氨酸、間甲酚、氯化鋅、濃縮彈酸、氫氧化鈉、注射用水)過敏者。

6. 特殊警語及使用注意事項
安全性摘要：Soliqua 治療期間最常見的不良反應為低血糖及胃腸道不良反應。Soliqua不可使用於第1型糖尿病病人或用於治療糖尿病酮酸中毒。
低血糖：Soliqua治療期間最常見的不良反應為低血糖。當Soliqua的給藥劑量高於需求量時可能導致低血糖。若病人具有低血糖感受性的風險因子，則應予以嚴密監測且有可能需調整劑量。Soliqua 的劑量應依照個人的臨床反應及病人對胰島素的需求作調整。低血糖的風險因子請詳見仿單。
急性胰臟炎：使用類升糖素肽狀-1(GLP-1)受體促效劑被認為與發生急性胰臟炎的風險相關。雖然尚未建立因果關係，但曾有使用lixisenatide發生急性胰臟炎的少數通報個案。應告知病人急性胰臟炎的特徵症狀；持續性的嚴重腹痛。若懷疑發生胰臟炎，應停用Soliqua，若確定為急性胰臟炎，lixisenatide不可重新投藥。有胰臟炎病史的病人使用時應小心。
嚴重胃腸道疾病：使用類升糖素肽狀-1(GLP-1)受體促效劑被認為與胃腸不良反應有關。Soliqua未曾針對嚴重胃腸道疾病病人做過研究，包括嚴重胃輕癱(gastroparesis)，因此Soliqua不建議使用於這類病人。
併用藥物：Lixisenatide 會延緩胃排空，因此可能會降低口服藥物之吸收速率，當病人接受的口服藥物必須經腸胃道快速吸收，或是需要仔細的臨床監測或是治療比狹窄(narrow therapeutic index)時，使用Soliqua應小心。
嚴重腎功能不全：尚無使用於嚴重腎功能不全 (肌酸酐廓清率< 30 mL/min)或末期腎病病人之治療經驗。本品不建議使用於嚴重腎功能不全或末期腎病病人 。
脫水：應告知病人，接受Soliqua治療有發生脫水的潛在風險，此與胃腸道不良反應有關，因此應小心以避免體液流失。
抗體形成：Soliqua注射有可能導致insulin glargine及/或lixisenatide抗體之形成。在早臭情況下，這類抗體的出現有可能需要調整Soliqua之劑量以避免高血糖或低血糖的發生。
避免用錯經路：應告知病人每次注射前都應檢查注射筆上的標籤以避免不小心拿錯Soliqua兩種不同單位含量之注射筆或與其他注射型糖尿病藥物混淆。為了避免劑量錯誤及可能發生過量，不論病人或醫療專業人員都不可以注射器抽取預填注射筆卡匣內的藥物。

7. 藥物交互作用
與其他藥物之交互作用或其他形式之交互作用：尚未以soliqua執行過藥物交互作用。以下資訊來自各別藥物的藥物交互作用資料。
Insulin glargine: 有些藥物可能會影響葡萄糖的代謝，因此可能需要調整insulin glargine的劑量。併用口服抗糖尿病藥、ACE抑制劑、dipyridamide、fibrates、fluoxetine、MAO抑制劑、pentoxifylline、propoxyphene、水楊酸鹽(Salicylates)、磺胺類(sulfonamide)的生素等，都可能會增加降血糖效果而容易造成低血糖症。併用皮質類固醇、danazol、diazoxide、利尿劑、glucagon、isoniazid、雌激素及黃體素(如口服避孕藥)、phenothiazine衍生物、somatropin、擬交感神經作用藥(如腎上腺素【adrenaline】、salbutamol、terbutaline)、甲狀腺荷爾蒙、非典型抗精神病藥物(如clozapin and olanzapine)或蛋白質酵素抑制劑可能會減弱降血糖效果。β-抑制劑、clonidine、鋰鹽或酒精可能會加強或減弱胰島素的降血糖效果；而pentamidine可能造成低血糖症，有時候又接著發生高血糖症。此外，β-抑制劑、clonidine、guanethidine、reserpine等藥物由於其交感神經抑制作用，可能會減弱或甚至完全抑制對上段反調節機制。
Lixisenatide: Lixisenatide是一種肽肽且不會被細胞色素P450所代謝。在體外試驗中，lixisenatide不會影響細胞色素P450同功酶或人體運輸蛋白(human transporters)的活性。Lyxumia延緩胃排空可能會降低口服藥物的吸收速率。當併用治療範圍狹窄或需要臨床上小心監測的口服藥物時應謹慎使用。與Lyxumia併用時，應適當監測這些藥物。若這些藥物要與食物併服，應告知病人盡量選擇未注射Lyxumia的那一餐或點心時間服用這些藥物。若口服藥物必須達到特定濃度閾值才具有療效，例如抗生素，或會造成延遲效果的藥物，例如acetaminophen，則併服該藥物時，必須至少在Lyxumia注射前1小時服用。使用口服避孕藥之病人，必須至少在lixisenatide注射前1小時或注射後11小時服用。
Acetaminophen (Paracetamol): Acetaminophen投與單一劑量1000mg後的暴露量(AUC)不受Lyxumia 10μg影響(不論在Lyxumia注射之前或之後)。當acetaminophen在Lyxumia注射前1小時給藥，acetaminophen的Cmax及tmax不受影響。當在lixisenatide 10 μg注射1小時或4小時後給藥，acetaminophen的Cmax分別下降了29%及31%，而tmax中位數則分別延後了2.0小時及1.75小時。
口服避孕藥
在Lyxumia 10 μg注射1小時前或注射11小時後給予單一劑量口服避孕藥(ethinylestradiol 0.03 mg /levonorgestrel 0.15 mg)，ethinylestradiol及levonorgestrel的Cmax、AUC、t1/2 及tmax皆不受影響。在Lyxumia 10 μg注射1小時或4小時後給予單一劑量口服避孕藥(ethinylestradiol 0.03 mg /levonorgestrel 0.15 mg)，ethinylestradiol及levonorgestrel的總暴露量(AUC)及排卵半衰期與 1/2不受影響，然而ethinylestradiol的Cmax分別降低了52%及39%，levonorgestrel的Cmax分別降低了46%及20%，tmax早位數則延後1-3小時。
Atorvastatin: 常Lyxumia 20 μg與atorvastatin 40 mg在早晨同時給藥6天，atorvastatin的總暴露量(AUC)不受影響，但Cmax會下降31%且tmax會延後3.25小時。若atorvastatin在傍晚給藥，Lyxumia在早晨注射，則atorvastatin的tmax未見延後，但AUC及Cmax 分別增加了27%及66%。Warfarin及其他coumarin衍生物Warfarin 25 mg與Lyxumia 20 μg重覆併用後，warfarin的AUC或國際標準化比值(INR)不受影響，但Cmax降低了19%且tmax延後了1小時。
Digoxin: Digoxin 0.25 mg與Lyxumia 20 μg併用後在穩定狀態下，digoxin的AUC不受影響，但digoxin的tmax延後了1.5小時，Cmax降低了26%。
Ramipril: Ramipril 5 mg與Lyxumia 20 μg併用6天後，ramipril的AUC增加了21%，Cmax則下降63%。其活性代謝物(ramiprilat)的AUC及Cmax不受影響。Ramipril及ramiprilat的tmax大約延後了2.5小時。

8. 生育能力、懷孕及哺乳
有關生殖力的資料：Soliqua不建議使用於有懷孕能力的未避孕婦女。
懷孕：尚無Soliqua、insulin glargine或lixisenatide 在對照性臨床試驗中使用於懷孕婦女之臨床資料。
哺乳：Insulin glargine或lixisenatide是否會從人類乳汁中分泌仍不得而知。Soliqua不可在哺乳期間使用。
生育能力：動物試驗並未顯示lixisenatide或insulin glargine會對生育能力造成直接傷害。

9. 過量
若病人的Soliqua給藥劑量高於需求量，則有可能發生低血糖及胃腸道不良反應。輕度的低血糖發作通常可給予口服碳水化合物治療。必要時可調整藥物劑量、膳食搭配或體能活動。伴隨昏迷、癲癇或神經受損的較嚴重低血糖發作可能必須給予升糖素之肌肉/皮下注射或濃縮葡萄糖液之靜脈注射。因為低血糖有可能在臨床上明顯改善後復發，因此必須持續給予碳水化合物並進行觀察。當有胃腸道不良反應時，應依病患的臨床徵兆及症狀給予適當的支持性治療。

10. 不良反應
Soliqua治療期間最常見的不良反應為低血糖及胃腸道不良反應。依臨床調查而得的以下相關不良反應是以全身器官分類並以發生頻率遞減的方式排列，概常見(≥1/10)：低血糖；常見(≥1/100~<1/10)：頭暈、噁心、腹瀉、嘔吐；不常見(≥1/1,000 ~ <1/100)：鼻咽炎、上呼吸道感染、荨麻疹、搔癢、消化不良、腹痛、疲倦、注射部位反應。詳細不良反應請見仿單。

11. 藥理學特性
藥理治療族群：治療糖尿病之藥物、胰島素及其類似物注射劑，長效型。ATC代碼：A10AE54。Soliqua內含作用機轉互補的兩種活性成分以改善血糖控制：Insulin glargine。它是一種基礎胰島素類似物(主要針對空腹血糖)及lixisenatide，此為類升糖素肽狀-1(GLP-1)受體促效劑(主要針對餐後血糖)。

Ref. SmPC_Jan-2017
藥品許可證字號：衛部菌疫輸字第001080號
製造廠Sanofi-Aventis Deutschland GmbH (Bruningstrasse 50, D-65926 Frankfurt am Main, Germany)
簡易仿單版本：Sep 2018
廠商：賽諾菲股份有限公司
地址：臺北市松仁路3號7樓
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北市衛藥廣字第107100393號

SATW.LAIL.18.10.0334(11/18)

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糖德仕注射劑

Toujeo 300 units/ml solution for injection

衛部菌疫輸字第 001011號

本藥須由醫師處方使用 處方資訊摘要 (詳細內容請參照衛生福利部核准之完整產品仿單)

適應症：

成人之糖尿病。

用法：

Toujeo以皮下注射方式給藥，注射部位為腹部、大腿或上臂三角肌，可於一天中任選某一時間注射，但固定於每天同一時間注射一次。必要時，病患可在平常注射時間提前或延後3小時內注射。

應依病患個別的代謝需求、血糖監測結果及血糖控制目標逐步調整Toujeo劑量。為使低血糖的風險降至最低，Toujeo的劑量應慢慢調整，每次調整至少應間隔3-4天。其它劑量使用的建議請詳閱藥品仿單。

禁忌症：

- 低血糖發作期間。
- 對insulin glargine或其中任何一種賦形劑過敏的病患。

警語及注意事項：

- Toujeo不適合用於治療糖尿病酮酸中毒患者。
- 病患之間不可共用Toujeo SoloStar注射筆。
- 兒童病患使用Toujeo的安全性及效果尚未建立。
- 肝功能不全或腎功能不全對Toujeo藥物動力學的影響尚無相關研究。接受Toujeo治療的肝功能不全或腎功能不全病患可能需要經常監測血糖並調整劑量。
- 絕對不可以使用注射器將Toujeo從SoloStar拋棄式胰島素預填注射筆中抽取出來。

交互作用：

會引起交互作用之藥物，請詳閱藥品仿單(May-2016)。

懷孕或授乳：

- 目前尚無懷孕婦女使用Toujeo的臨床研究。從懷孕婦女所取得的大量數據(超過1000位孕婦使用Lantus的結果)顯示，insulin glargine對於懷孕無特定的不良影響，也沒有特定的畸形或胎兒/新生兒毒性。因為動物生殖毒性試驗並無法完全預測人類對藥品的反應，因此，只有在Toujeo對於胎兒的好處高於胎兒的風險時，才可以於懷孕期間使用Toujeo。
- 內生性胰島素會出現在人類乳汁中; insulin glargine是否會分泌於人類乳汁則尚不清楚。因為許多藥物，包括人類胰島素，都會從人類乳汁中排泄，因此哺乳婦女使用Toujeo時應小心。Toujeo可以在哺乳時使用，但糖尿病婦女授乳時可能需要調整胰島素的劑量。

不良反應：

- 低血糖、過敏或過敏反應、低血鉀、周邊水腫、 脂肪代謝障礙、體重增加。

* 對於併用非胰島素降血糖藥物或併用餐前胰島素治療之第2型糖尿病患者，從第9週至試驗結束這段期間，在降低已確認之夜間低血糖的發生風險上為Toujeo治療組優於Lantus治療組，患者是第2型糖尿病接受基礎胰島素治療且併用餐前胰島素(風險降低21%)

Reference：

1. Yki-Jarvinen H, et al. (Poster #946) presented at EASD, Vienna, September 15–19 2014. Available from: http://www.easdvirtualmeeting.org/ resources/19180. Date accessed: April 2015
2. Riddle MC, et al. Diabetes Obes Metab. DOI: 10.1111/dom.12472. epub 2015.
3. Bergenstal R, et al. (Poster #949) presented at EASD, Vienna, September 15–19 2014. Available from: http://www.easdvirtualmeeting.org/resources/18574. Date accessed: April 2015.
4. Yki-Jarvinen H, et al. Diabetes Care 2014;37:3235–3243.
5. Becker RH, et al. Diabetes Care 2015;38(4):637–643.

製造廠：Sanofi-Aventis Deutschland GmbH
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Toujeo®
insulin glargine 300U/mL

北市衛藥廣字第106100371號
處方前請詳閱藥品仿單，詳細處方資料備索

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SATW.TJO.17.07.0195 (09/17)

Depakine®

Sodium Valproate/Valproic Acid

帝拔癇持續性藥效膜衣錠 500 毫克

【組成】每錠含 Sodium Valproate 333 mg，Valproic Acid 145 mg。主成分相當於 Sodium Valproate 500 mg 為有刻痕的錠劑（Scored Tablet）。【適應症】癲癇之大發作、小發作、混合型及顳葉癲癇；躁病。【用法用量】詳細內容請參照仿單。本藥須由醫師處方使用。癲癇 本藥劑量適用於成人及體重 17 公斤以上之兒童。本藥不適用於六歲以下的孩童。起始日劑量通常為 10-15mg / kg，而後增加到適當的劑量每日平均劑量為 20 - 30 mg / kg。但若病情在此劑量下未能充份控制，可能要增加劑量並密切觀察。兒童的常用劑量為每天 30 mg / kg。成人的常用劑量為每天 20 - 30 mg / kg 用法 口服使用。每日劑量分一至二次服用，建議與餐點同時服用。對於控制良好的癲癇病人，建議一天服藥一次。吞服本藥時不可壓碎或咬碎錠劑。開始使用 sodium valproate 治療-若以持續性藥效錠取代 sodium valproate 的一般錠劑時，在病情控制下，建議維持原先使用之日劑量。-若病人已服用其他抗癲癇藥物治療時，應以漸進方式逐漸加入 sodium valproate，在二星期內增加至最適當的劑量，若有需要，原先的抗癲癇藥物可在病情控制下慢慢減量。沒有服用其它抗癲癇藥物的病人：每隔 2 到 3 天逐次增加 sodium valproate 的劑量，約在一星期內可達到最適當的治療劑量。如果須要加入其他的抗癲癇藥物，應以漸進方式逐漸加入。躁病 建議以日劑量 600 mg 開始給藥，再以日劑量 200 mg，每三天為間隔。逐步增加劑量至病情被控制為止。一般劑量範圍為 1000 mg / day 到 2000 mg / day (即 20 - 30 mg / kg)，若在此劑量範圍內仍未能控制病情，可增加劑量至最高 2500 mg / day。【說明】詳細內容請參照仿單。癲癇成人及兒童:可以單藥治療或與其他抗癲癇藥物併用治療下列癲癇：1. 全面性癲癇發作：陣攣性癲癇發作、強直性癲癇發作、大發作、小發作、肌陣攣性或失張性癲癇發作、Lennox-Gastaut 症候群。2. 局部性癲癇發作：局部性癲癇發作或局部性癲癇發作後繼發全面性癲癇發作。【禁忌】治療癲癇：在懷孕狀態下，除非沒有適合的替代療法。具有生育能力的婦女，除非能確實履行避孕計畫。治療躁鬱症: 在懷孕狀態下。具有生育能力的婦女，除非能確實履行避孕計畫。對 valproate、divalproate、valpromide 或本品其他成份過敏者。急性肝炎患者。慢性肝炎患者。有嚴重肝炎之個人或家族病史者，特別是藥物引起的肝炎。肝性吡咯紫質沉著症（hepatic porphyria）。和 mefloquite 合併使用和 St.-John's-Wort 合併使用。已知由粒線體聚合酶γ基因突變所致粒線體疾病的患者（POLG, 例如 Alpers-Huttenlocher Syndrome）以及臨床上懷疑有 POLG 相關疾病的兩歲以下兒童。尿素循環代謝異常者。【警語】詳細內容請參照仿單。開始使用抗癲癇藥物治療，在極罕見的情況下，病人可能會發生更嚴重之癲癇發作，或產生新的癲癇發作形態。對於女性兒童、具生育能力的女性本品必須在具有處理癲癇或雙極性精神障礙經驗的專家監督下使用。本品使用於孕婦可能傷害胎兒，孕婦使用本品可能造成胎兒神經管缺陷和其他結構異常。使用本品可能導致孩童有較低的智商。除非因醫療考量必要使用，否則不應使用於具生育能力或有懷孕可能性之婦女。特別是被使用在不會伴有永久性傷害或死亡（例如偏頭痛）的情況下。女性在使用本品時應有效避孕。而對於有計畫懷孕的婦女，應告知使用本品之風險與治療效益，並考慮使用其他替代療法。Valproate 有高度的致畸性，且胎兒在子宮中曝露於 valproate 有導致先天性畸形和神經發育缺陷的高度風險。Valproate 治療開始時和專科醫師對 valproate 治療進行年度評估期間，以及當婦女準備懷孕或已懷孕時，都應使用風險確認評估表。本藥不建議與lamotrigine 和 carbapenem 製劑併用。【交互作用】不可併用：mefloquite。不建議併用：Lamotrigine。【不良反應】詳細內容請參照仿單。檔常見（_ 10%）：噁心、震顫。常見（_ 1%，< 10%）：貧血、血小板減少、錐體外系統失調、麻木、嗜睡、癡睡、記憶力衰退、頭痛、眼球震顫、頭暈、聽力喪失、嘔吐、齒齦疾病(主要為齒齦增生)、口腔炎、上腹部疼痛、腹瀉、尿失禁、過敏、暫時性和/或與劑量相關之掉髮、指甲與甲床疾病、低血鈉、體重增加、出血、肝臟損傷、經痛、意識混亂、幻覺、侵略性、激動、注意力障礙。不常見（_ 0.1%，< 1%）：胰臟炎,有時有致命性。罕見（_ 0.01%，< 0.1%）：毒性表皮溶解、Steven-Johnson 症候群、多形性紅斑、伴隨嗜伊紅性白血球增加與全身症狀的藥物反應（DRESS）。其他發生率不常見、罕見、檔罕見（< 0.01%）之不良反應請參照仿單。【過量】詳細內容請參照仿單。急性的 valproate 過量所引起的臨床症狀為不同深淺度的昏迷伴有肌肉張力降低、反射減弱、縮瞳、自主性的呼吸減弱及代謝性酸中毒、低血壓及循環性虛脫/休克。在非常高的血漿濃度下，曾被報告過有癲癇發作。有少數因腦水腫導致顱內高血壓的病例亦曾被報告過。鈉含量存在於 valproate 組成分中，當服用過量時可能會導致高鈉血症。醫院對藥物過量的處理應包括：若需要時可進行洗胃、維持有效的利尿、並監測心臟和呼吸系統功能。在極嚴重的病例可能須進行腎臟透析。一般過量之慮後尚佳，但也有因過量而致死的案例被報告過。仿單版本：CCDS v25

處方前請詳閱藥品仿單，詳細處方資料備索。

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*on top of maximally tolerated dose of statin

創新作用機轉
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Praluent 保脂通注射劑 75 毫克　衛部菌疫輸字第 001037 號　簡易處方摘要 EMA+CCDS v3_12 May 2016+v4_06 Oct 2017+Q4W+ToR+KT study

【藥品名稱】保脂通注射劑 75 毫克預填注射筆 (針筒)。【定性定量組成】75 mg/ml 注射用溶液。單次使用的預填注射筆 (針筒) 中，每 1 毫升溶液含有 alirocumab 75 毫克。【適應症】(1) 對於已接受最高耐受劑量 statin，但低密度脂蛋白膽固醇 (LDL-C) 仍無法達到目標值之異合子家族性高膽固醇血症 (HeFH) 或動脈粥狀硬化心血管疾病 (clinical ASCVD) 之成人患者，Praluent 可作為飲食外的輔助治療。(2) 對 statin 不耐受或禁用 statin 之原發性高膽固醇血症 (異合子家族性及非家族性) 或混合型血脂異常之成人患者，Praluent 可單獨或併用其他降血脂藥物，作為飲食外的輔助治療。Praluent 對心血管事件發病率及死亡率的影響尚無法確定。【用法用量】在開始 Praluent 治療前，應先排除高血脂症或混合型血脂異常之次要病因 (例如，腎病症候群、甲狀腺功能低下)。Praluent的建議起始劑量為 75 毫克，每 2 週一次，或 300mg 每 4 週(每月)一次，以皮下注射給藥。多數的患者在此劑量下能使低密度脂蛋白膽固醇 (LDL-C)充分下降。若 LDL-C 的反應不如預期，則可調整至最高劑量 150 毫克，每 2 週皮下注射一次。Praluent 之劑量可依個別病患之特性調整，如：LDL-C基期濃度、治療目標及對治療的反應。血脂濃度可於治療開始或劑量調整後 4-8 週進行評估並隨之調整劑量 (增加劑量或減少劑量)。病患應給予最低必要劑量，以達到 LDL-C 所希望之降低程度。若病患已接受 75mg 每 2 週一次或 300 mg 每 4 週(每月)一次之治療，但 LDL-C 需要再度降低者，可將劑量調整至 150 mg 每 2 週一次之最高劑量。若漏打每2週一次劑量，病患應儘快於漏打後七天內補打該次藥物，並依原注射時程繼續治療。若未能於漏打後七天內補打該次注射藥物，則不須補打，依原注射時程繼續治療。若漏打每 4 週(每月)一次劑量，病患應儘快於漏打後七天內補打該次藥物，並依原注射時程繼續治療。若未能於漏打後七天內補打該次注射藥物，則於發現漏打時補打，並重新開始新的療程。【禁忌】對活性成分或組胺酸(Histidine)、蔗糖、聚山梨醇酯20 (Polysorbate 20)、注射用水等賦形劑過敏者。【警語及注意事項】若有嚴重過敏反應之徵兆或症狀(包括搔癢，以及罕見但有時嚴重的過敏反應如:錢幣狀濕疹、蕁麻疹及過敏性血管炎)出現，Praluent 應停用並給予適當的症狀性治療。重度腎功能不全的患者使用時應小心。重度肝功能不全的患者使用時應小心。【懷孕及哺乳】除非婦女的臨床狀況需要接受 alirocumab 治療，否則懷孕期間不建議使用。因為 alirocumab 對於吸吮母乳之嬰兒的影響尚不清楚，因此這段期間應決定是停止哺乳或停用 Praluent 治療。【不良作用】最常見的不良反應為局部注射部位反應、上呼吸道徵兆與症狀，以及搔癢。導致病患停用 Praluent 治療的最常見不良反應為局部注射部位反應。【其他藥物對 alirocumab 的影響】Statins 及其他血脂調節藥物已知會增加 PCSK9 蛋白之生成，此蛋白質為 alirocumab 之作用標的。這會導致標的調節性廓清率增加並降低了 alirocumab 的全身曝藥量。Alirocumab 與 statins、ezetimibe 及 fenofibrate 併用時，alirocumab 的曝藥量比其單藥治療時的曝藥量降低了 40%、15% 及 35%。【藥理治療族群】：其他血脂調節劑。 ATC 代碼：C10AX14。詳細資訊請參閱衛生福利部核准之完整說明書內容。

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使用前詳閱說明警語及注意事項
PSST-TW-2018-018-AA, June 2018

福退癌® 膜衣錠 200 毫克

Votrient® (Pazopanib HCL) film-coated tablets 200 mg

適應症與用法：晚期腎細胞癌之第一線治療，或用於已接受細胞激素 (cytokine) 治療失敗之晚期腎細胞癌患者。

建議劑量：Votrient® 之建議劑量為一天一次，空腹時口服 800 mg（至少於用餐前 1 小時或用餐後 2 小時）。Votrient® 之劑量不應超過 800 mg。請勿壓碎藥錠，因為可能會增加吸收速率而影響全身暴露量。當漏服一劑時，如果與下次服藥時間的間隔小於 12 個小時，請勿補服。

劑量調整：對於腎細胞癌患者，初次劑量調降時應調整為 400 mg，接續的劑量減少或增加應根據個別患者的耐受性，每次調整 200 mg。肝功能不全：輕度肝功能不全患者無須調整劑量。中度肝功能不全患者則應考慮以其他藥物替代 Votrient®，若仍有臨床上的需求，劑量應調降至每日 200 mg；不建議使用 Votrient® 治療重度肝功能不全患者。併用強效的 CYP3A4 抑制劑：併用強效的 CYP3A4 抑制劑（例如：ketoconazole、ritonavir、clarithromycin）可能會增加 pazopanib 的濃度，故應避免合併使用。考慮以其他無或幾乎無 CYP3A4 抑制效果的藥物替代。若必須併用強效的 CYP3A4 抑制劑，則 Votrient® 的劑量應降低至 400 mg。若治療過程發生不良作用，可能需要進一步降低劑量。併用強效的 CYP3A4 誘導劑：併用強效的 CYP3A4 誘導劑（例如：rifampin）可能會減少 pazopanib 的濃度，故應避免合併使用。考慮以其他無或幾乎無酵素誘導效果的藥物替代。若無法避免而需長期服用強效 CYP3A4 誘導劑的患者，則不應使用 Votrient®。

不良反應：常發生的不良反應為腹瀉、高血壓、髮色改變、噁心、疲勞、食慾不振、嘔吐。

警　　語：肝毒性。臨床試驗中曾觀察到嚴重且致命的肝毒性。應依建議監測肝功能，必要時應暫停使用、減量或停用藥物。

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使用前詳閱說明書、警語及注意事項
詳細資料備索

Reference: VOTRIENT [summary of product characteristics]. Camberley, UK: Novartis Europharm Limited; June 2015.

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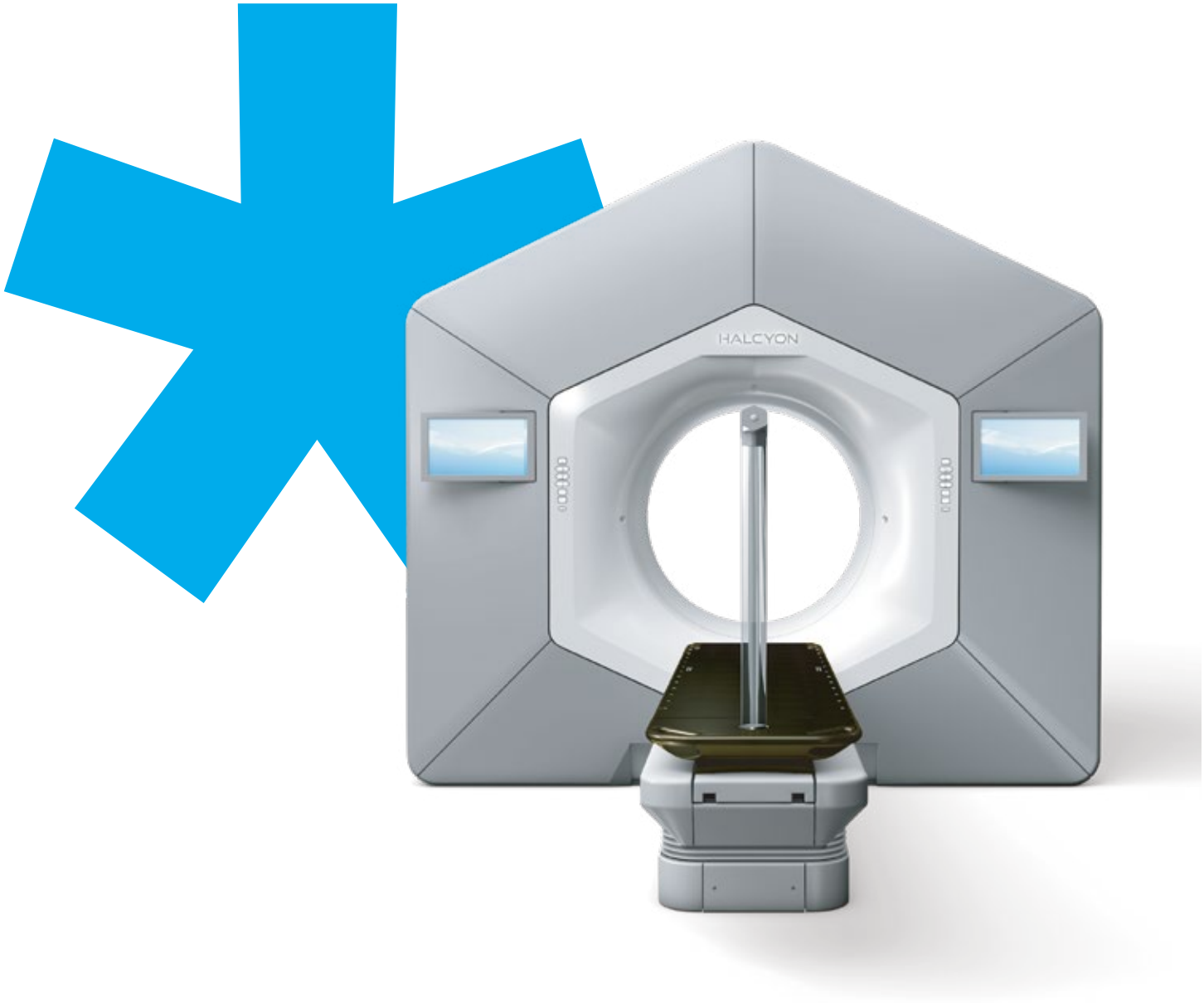
HALCYON™



* Transformative radiotherapy that's not only making advancements, but making a difference.

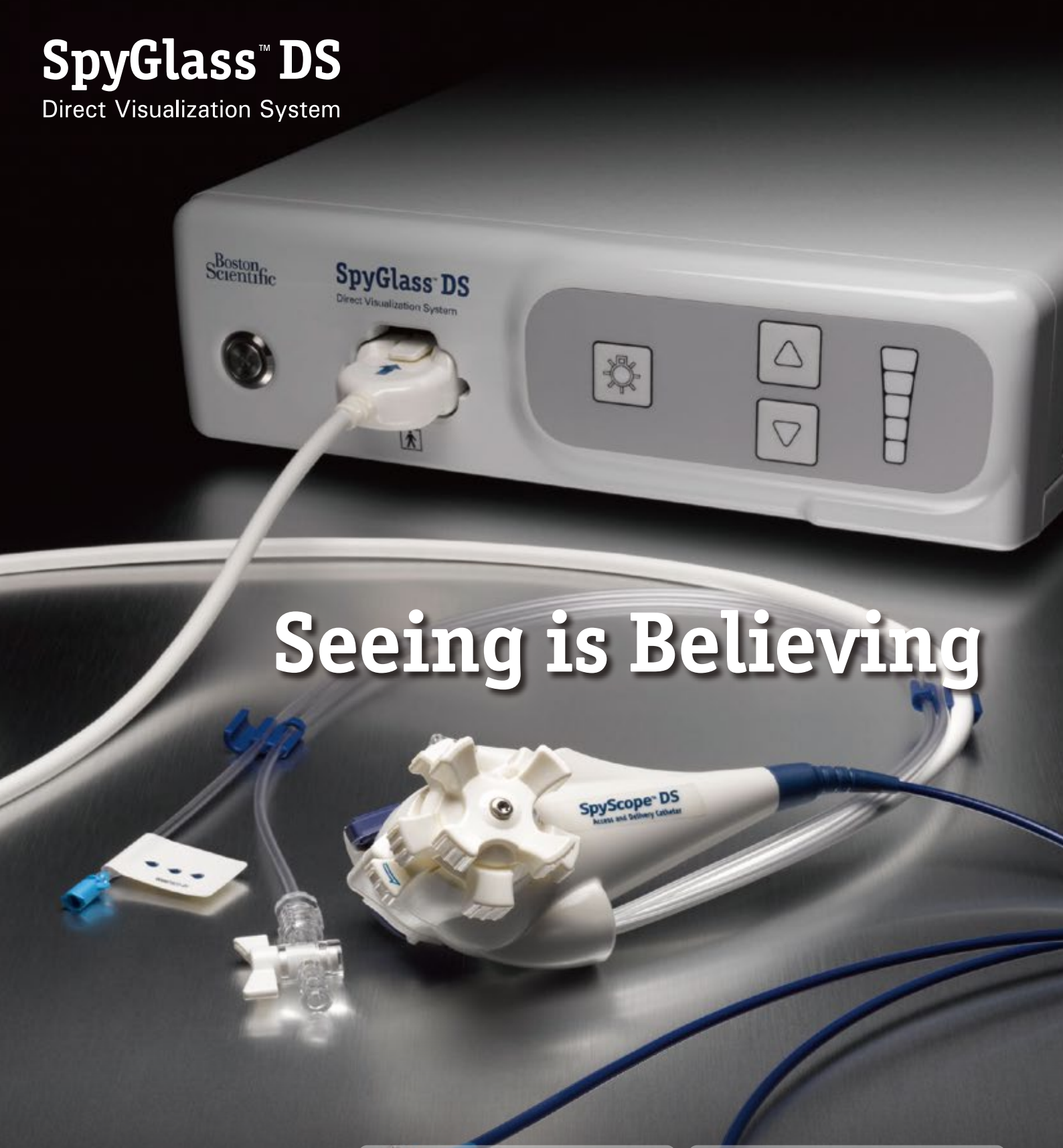
The Halcyon™ radiotherapy system was built to transform the way the world thinks about fighting cancer. With an intuitive workflow, image-guided precision, and reduced treatment time, Halcyon provides more opportunities to deliver more care to more patients—because new victories in the cancer fight matter now more than ever.

Safety information: Radiation may cause side effects and may not be appropriate for all cancers.

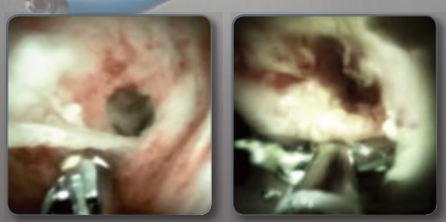
varian

SpyGlass™ DS

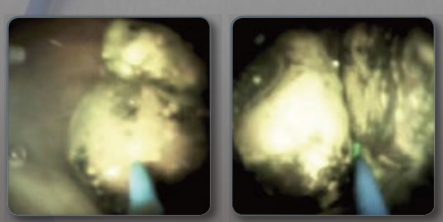
Direct Visualization System



Seeing is Believing



Taking biopsies under direct visualization using miniature SpyBite Forceps



Fragmenting a large biliary stone using a holmium laser probe with SpyGlass DS System

Boston Scientific

Delivering what's next.™

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號及衛署醫器輸壹字第 009786 號
北市衛器廣字第 107060380 號
使用前詳閱說明警語及注意事項
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