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暨聯合學術研討會

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腫瘤及細胞治療的最新進展

The Latest Progress of Cancer and Cell Therapies

時　間：107年6月30日　　08:15~12:20
Time：June 30, 2018　　08:15~12:20

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

腫瘤及細胞治療的最新進展

The Latest Progress of Cancer and Cell Therapies

Local immunotherapy

局部免疫治療

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Immune checkpoint-targeted monoclonal antibodies are successful in the treatment of many types of cancers. By blocking programmed death receptor 1 (PD-1), programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4), T cells are re-activated leading durable cancer immunity. In spite of the survival benefit over conventional therapies, only a subset of patients develop an objective tumor response with long-term survival benefits. Moreover, the systemic delivery of immunotherapies may cause severe toxicity that is so-called immune-related adverse event (irAE).

Local immunotherapy is a therapeutic strategy which aims to achieve local tumor control, trigger tumor-specific immunity by using tumor as its own vaccine and control systemic disease. Using direct injection, a high concentration of immune stimulatory products can be achieved with only a small amount of drug. Local immunotherapy also allows combination and multiple injections. Systemic anti-tumor immunity (abscopal effect) could be induced without significant systemic off-target toxicities.

While addressing many of the current limitations of systemic immunotherapy, local immunotherapy may offer a different approach to control tumors. Especially for those locally advanced tumor, local immunotherapy may provide the chance to turn inoperable tumors into operable tumors.

The predictive biomarkers for cancer immunotherapy

腫瘤免疫治療療效的預測因子

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Although immune checkpoint inhibitor had made huge progress in cancer treatment, relatively low response rate makes predictive biomarker an unmet need and is worthy investigating.

The PD-L1 expression from pathology sample once the most popular biomarkers for PD-1 checkpoint inhibitor. MSI status and tumor mutation burden are reported to provide fair predictive power. FDA then approved anti-PD-1 therapy in solid tumor patients with high MSI status. Interferon gamma pathway also showed some impact to the response in these treatment. However heterogeneity and the dynamic change make it difficult to predict precisely when tools which based on pathology. Furthermore, the microbiome of patients may also influence the response of immunotherapy.

To sum up, optimal biomarkers for immunotherapy may not yet emerge at this time. However investigators are working with it and hopefully will improve the treatment outcome in the future.

Targeting immune checkpoints : Strategy other than antibody?

針對免疫調控點：抗體以外的策略？

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Increasing numbers of antibodies against immune checkpoints such as CTLA-4, PD-1, and PD-L1 have gained regulatory approval and displayed notable efficacy as well as durable responses in subsets of patients with various malignancies. Immune checkpoints as promising anticancer drug targets have generated great interest within both academia and the biopharmaceutical industry. In addition to antibodies as the mainstream therapeutics against immune checkpoints, several strategies have also been under investigation to modulate the immune system for cancer treatment. Our group had previously developed vaccines against CTLA-4 and PD-L1, capable of eliciting antibodies specific to these two immune checkpoints. In the experimental mice, the immune reactivity for CTLA-4 and PD-L1 was sufficient for inhibiting B16F10 and LLC tumor growth in c57BL/6 mice without measurable toxicity. The growing amount of crystal structures for PD-1, PD-L1, and their antibodies has led to the attempt in developing small chemical inhibitors interrupting these pathways. Moreover, several compounds have been demonstrated to affect either the expression or stability of these immune checkpoints. In this presentation, we will discuss some of the progress made by our and other groups in these strategies.

Clinical application of immunotherapy for advanced gastric cancer in Kyushu University

免疫療法用於晚期胃癌的臨床應用

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Molecular targeted drugs and immune checkpoint inhibitors have been developed for advanced gastric cancer (AGC). In the Japanese Gastric Cancer Treatment Guideline 2018 (version 5), in combination with cytotoxic drugs, anti-Her2 antibody for Her2-positive AGC in first-line therapy and anti-VEGFR2 antibody in second-line therapy are recommended. Based on the recent Asian phase 3 clinical study, a monotherapy of anti-PD-1 antibody has been recognized a standard in salvage chemotherapy for AGC. However, effective predictive biomarkers for the therapy have still not been established. The Cancer Genome Atlas proposed four molecular classification of GC by employing comprehensive molecular evaluation (Nature 513, 202-9, 2014): Epstein-Barr virus-positive (EBV); microsatellite unstable (MSI); genomically stable (GS); and tumors with chromosomal instability (CIN). Favorable efficacy of immune checkpoint inhibitors are expected in EBV-group GC preferentially expressing PD-L1/L2 and in MSI-group GC harboring elevated mutation rates. CIN-group GC characterized by gene amplification of receptor tyrosine kinases might require multiple targeted therapy because of heterogeneity. GS-group GC preferentially shows diffuse histology in association with RHOA, CDH1 mutations, which might be targets for novel therapy. Because of expanding new precision medicine policy from this year in Japan, accelerated development of therapeutic strategies for AGC including immunotherapy is expected.

Recent advances in cancer vaccine and cell immunotherapy

腫瘤疫苗及免疫細胞治療的最新進展

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Cancer immunotherapy mainly includes cancer vaccines, immune cell therapy, and modulation of immune system of the patients, such as antibody to checkpoint(PD-1 or PDL-1.etc). Tumor has many somatic mutations, and these mutations may generate cancer-specific neoantigens, and can be distinguished by T cells as a foreign body which is an ideal vaccine target. Every tumor has many unique mutations, and only a small portion shared between cancer patients. These unique mutation-related cancer-specific neoantigens are the central part of cancer immunotherapy. Thanks to the technological advances in next generation sequencing, data science and artificial intelligence, cancer immunotherapy can use these tools to select vaccine targets and produce a personalized therapy. In this report, I am going to introduce recent advances in these fields, especially focus on cancer vaccines.

CAR-T cell therapy: Progress and prospects

CAR-T 在癌症治療的最新進展

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Patients with relapsed or refractory acute lymphoblastic leukemia have a poor prognosis due to resistance to salvage treatments such as chemotherapy and hematopoietic stem cell transplantation. Recently, durable long-term complete remissions have been demonstrated in patients with B-cell malignancies receiving infusions of CD19 specific chimeric antigen receptor (CAR)-T cells. The editors of Science Journal have announced cancer immunotherapy as the breakthrough of the year for 2013. In 2015, Dr. Steven M. Altschuler, the chief executive officer of the Children's Hospital of Philadelphia and 9-year-old ALL patient Emily Whitehead with 3-year leukemia-free after CAR-T cell infusion were invited to White House for President Barack Obama's announcement of the Precision Medicine Initiative.

The Food and Drug Administration (FDA) made history by approving Kymriah, the first living drug, for childhood leukemia treatment on August 30, 2017. However, CD19-positive or -negative relapses due to poor T-cell persistence or CD19 antigen escapes have occurred in about half of the patients receiving CD19 CAR-T immunotherapy. As we learned from chemotherapy, prevention of leukemia relapse required multiple agents. The same concept may be right for immunotherapy. For relapse associated with CD19-negative clone selection or down-regulation, using a single CAR construct incorporating CD19/CD20 or CD19/CD22 for dual targeting could prove more effective at reducing relapse associated with antigen escape. Clinical trials testing bispecific CAR are underway.

Compared to the excellent response to CAR-T immunotherapy in patients with B-malignancies, inadequate responses were noted in patients with solid tumors. The discordant clinical outcomes between B-malignancies and solid tumors treated with CAR-T cells remains a challenge needed to be solved due to potential toxicity of on-target recognition of normal tissues, the heterogeneous expression of a target antigen and the hostile tumor microenvironment. Several new approaches are emerging to overcome these hurdles.

Application of immunoprofiling as a predictive biomarker for immunotherapy to advanced cancer

免疫細胞型態功能分析作為惡性腫瘤免疫療法之預測因子的應用

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As immunotherapy was becoming more prominent in cancer treatment, immune cell profile changes should be efficiently monitored to correlate with clinical performance. By taking advantages of a screening platform using more than 60 epitope-specific antibodies and flow cytometry to identify more than 400 cell subsets in peripheries of healthy subjects, current study show that peripheral immune cell profiles of HCC patients expressed a unique pattern distinguished from healthy subjects. Further calculation of immune scores specific for HCC by transformation of variable differences of affected peripheral immune cell subsets for the first time was proven as a feasible tool to diagnose HCC. After Nivolumab treatment, three subjects (19%) carried partial responses (PR) and nine subjects (56%) carried stable diseases (SD). The overall response rate was 19%, and the disease control rate (CR+PR+SD) was 75%. The median time to progression was 2.7 months. Importantly, subsequent retrospective comparison of cancer immune scores of HCC subjects with PD and PR before treatment indicated of worse immune scores by HCC with PD than those with PR, and this finding endowed Nivolumab treatment with a practical Biomarker to enroll susceptible cancer victims. Simultaneously determination of MSI, however did not support MSI-H as a predictive Biomarker for HCC victims to receive Nivolumab treatment. Continuous comparison of peripheral immune profiles of HCC with PR and PD after treatment showed that Nivolumab treatment mounted efficient anti-cancer immune responses (HCC with PR) by dampening $CD14^+$ monocytes, PD-$L1^+$ NKT cells, but promoting $CD4^+$ ($Foxp3^+CD25^+$) Treg cells at peripheries. Further combing changes of above mentioned 4 immune cell subsets indicated that HCC with PD increased changes in folds but HCC with PR decreased changes in folds, implying immune profiling of 4 selective immune subsets might serve as prognostic Biomarkers for Nivolumab treatment. All together with, current novel cancer immune profiling and scoring system might efficiently identify susceptible victims as predictive Biomarkers and validate therapeutic benefits as prognostic Biomarkers for Nivolumab treatment.

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肝癌治療新展望

A New Landscape of HCC Treatment

主辦單位：中華醫學會
協辦單位：臺灣消化系醫學會、臺灣肝臟研究學會、
臺灣肝癌醫學會、臺灣腫瘤消融醫學會

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肝癌治療新展望
A New Landscape of HCC Treatment

The impact of direct-acting antivirals for chronic hepatitis C on the development and recurrence of HCC

C 型肝炎直接對抗病毒藥物對於肝癌發生以及復發之影響

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Chronic hepatitis C (CHC) is the major etiology of liver cirrhosis, and hepatocellular carcinoma (HCC) in the world. Active viral replication is associated with a higher risk of HCC development for patients with chronic viral hepatitis. Anti-viral therapy can suppress viral replication, ameliorate liver inflammation, regress hepatic fibrosis, and preserve liver function. Interferon (IFN) and ribavirin (RBV) combination therapy have been regarded as the standard of treatment for CHC in the past decades. Previous studies demonstrated that IFN-based antiviral therapy could reduce the risk of HCC development in patients with CHC. Moreover, it could also decrease the rate of late recurrence of HCV-related HCC after curative therapies. However, IFN and RBV combination therapy has several side effects, such as flu-like syndrome, depression, bone marrow suppression, hemolytic anemia, and abnormal thyroid function and glucose levels during therapy. Moreover, IFN based regimens are contra-indicated for patients with decompensated cirrhosis. Direct antivials (DAAs) have been widely applied for the treatment of CHC. For patients with cirrhosis, DAAs could provide an excellent viral suppression efficacy and safety profile, even in the setting of liver decompensation. Moreover, treated patients had a significantly improvement in liver functional reserve after therapy. However, one active debating issue is that for patients with chronic hepatitis C and liver cirrhosis, whether DAAs would increase the risk of HCC development and recurrence after curative therapies for HCC. Further prospective studies are warranted to elucidate this issue.

Cancer staging in hepatocellular carcinoma: An embarrassment of riches

肝癌分期：富有的窘境

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Hepatocellular carcinoma (HCC) is a major cancer worldwide, accounting for more than 700,000 deaths each year. The highest incidence rates of HCC are in Southeast Asia and sub-Saharan Africa where hepatitis B virus infection is endemic. The incidence of HCC in the United States has also tripled in the past two decades due to chronic hepatitis C virus infection. The management and prognosis of HCC depend not only on tumor burden alone but also on underlying liver functional reserve. Identifying important clinical predictors is crucial in developing a robust staging system. The key predictors of prognosis in HCC patients include severity of liver dysfunction, tumor extent, overall health status and treatment modality. The Barcelona Clínic Liver Cancer (BCLC) staging system incorporates these key factors and includes treatment suggestions for different stages. The BCLC system has been integrated in the current American Association for the Study of Liver Diseases and European Association for the Study of the Liver HCC management guidelines. The recently proposed Hong Kong Liver Cancer (HKLC) staging system offered better prognostic ability and a more aggressive treatment algorithm compared with BCLC system. However, the capability of HKLC in a European cohort has been challenged. Besides the BCLC and HKLC systems, multiple staging systems were proposed without the ability to guide treatment decisions directly. These systems generally claimed to have superior prognostic performance. To date, at least 12 prognostic models have been proposed. The pursuits of an optimal staging system for HCC have resulted in heated debates for the past 2 decades. This lack of consensus may stem from heterogeneity of underlying liver diseases as well as diverse preferences of treatment modalities worldwide. The absence of a consensus on cancer staging may further hinder clinical researches from adequate disease control. This presentation will comprehensively review the current status of these staging systems. In summary, BCLC is the currently used system but has intrinsic deficiencies. Tumor burden, severity of cirrhosis and performance status determine overall survival. Treatment strategy-based staging system is required, and incorporation of new biomarker into the prognostic model is mandatory.

Yttrium-90 selective internal radiation therapy (SIRT) versus transcatheter arterial chemoembolization (TACE) for HCC

釔 90 微球體體內放射治療術與栓塞化學治療術對於肝癌治療療效之比較

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The mechanism of SIRT differs from chemoembolization. TACE relies on the occlusion of vessels feeding the tumor, thus allowing stasis and hence maximum exposure of the chemotherapeutic agent to the ischemic environment created within the tumor. In contrast, blood flow into the tumor is required for SIRT to allow free oxygen radical generation via the ionization of water molecules from the emitted β-radiation. The ideal candidates for TACE and SIRT are different and it is very difficult to conduct a prospective, head-to-head study comparing TACE vs SIRT.

Up to now, all studies comparing SIRT with TACE have been retrospective with a small number of patients. Comparing to TACE, SIRT induced less toxicity, and provided significantly longer time to progression. In a small series, SIRT showed better tumor control and a higher proportion received liver transplantation than those with TACE. Since TACE is reimbursable in Taiwan, most of SIRT cases at Taipei Veterans General Hospital were unsuitable for TACE or progressed after 2 times of TACE. As at 30 Sep, 107 patients enrolled in the RESIN registry (REgistry of Selective Internal Radiation Therapy in TaiwaN) from 7 different medical centers. The registry data provides a real-world view of clinical practice, patient outcomes and safety.

Advances in targeted therapy for HCC

肝癌標靶治療之新進展

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Sorafenib, which was shown to improve survival in the SHARP and Asia-Pacific trials, has been the standard therapy for unresectable hepatocellular carcinoma (HCC) since 2007. Since then, several first-line clinical trials have been conducted with the aim of developing molecular targeted agents showing better efficacy or safety than sorafenib.

Amid many failed trials of the 1st line agent, the results of a phase III trial of lenvatinib were presented at ASCO 2017. The trial met the primary endpoint of noninferiority, a shocking result that produced the greatest breakthrough in 10 years, suggesting a new option for first line molecular targeted therapy. Another recent development was the improvement in progression-free survival (PFS) achieved with sorafenib plus transcatheter arterial chemoembolization (TACE), as this approach was extremely challenging to develop.

At the European Society of Medical Oncology World Congress of Gastrointestinal Cancer held in Barcelona, Spain, on 30th June 2016, positive outcomes were reported by the RESORCE trial, which investigated the efficacy of regorafenib as 2nd line therapy after sorafenib failure. In this clinical trial, the group who received regorafenib achieved a survival benefit of approximately 2.8 months compared to the placebo group. Overall survival (OS) was 10.6 months in the regorafenib arm compared with 7.8 months in the placebo arm, with a hazard ratio (HR) of 0.62 (95% confidence interval [CI]: 0.50–0.78; $p<0.001$). These are groundbreaking results. The positive outcome achieved by this second-line systemic therapy is a major development, especially after the numerous reports of failures in clinical studies of first - and second - line systemictherapeutic agents. Regorafenib therapy is expected to significantly prolong life expectancy by approximately 2.8 months in patients with HCC who develop progressive disease during sorafenib therapy. This development will certainly lead to drastic changes in the treatment strategy and management paradigm for HCC.

The results of the phase III trial of cabozantinib was presented at ASCO-GI in 2018. This resulted in significantly better OS in the cabozantinib group (10.2 months, 95% CI: 9.1--12.0) than in the placebo group (8.2 months, 95% CI: 9.1--12.0) and consequently in a positive result for the clinical trial. PFS, the secondary endpoint, was also better in the cabozantinib group (5.2 months, 95% CI: 4.0--5.5) than in the placebo group (1.9 months, 95% CI: 1.9--1.9).

As a result, currently, we have 2 1st line agents, sorafenib and lenvatinib, and 2 2nd line agents, regorafenib and cabozantinib. How to use these agents for HCC patients in clinical prectice is the issue to discuss.

Sorafenib treatment for HCC: Taiwan experience

肝癌病患使用蕾莎瓦治療的台灣經驗

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Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed and the second most lethal cancer worldwide, leading to approximately 600,000 deaths each year. HCC is prevalent in East Asia and sub-Saharan Africa, an endemic area of hepatitis B virus (HBV) and hepatitis C virus infection with the incidence rates of more than 20 per 100,000 persons. Despite the advances in surveillance and HBV vaccination, a large number of cases are still at an unresectable, advanced stage and require systemic treatment.

Sorafenib, a multi-kinase inhibitor that inhibits tumor-cell proliferation and angiogenesis, has been proved to prolong both progression-free survival (PFS) and overall survival (OS) in advanced HCC. However, the efficacy of sorafenib is still modest; and the median time to progression ranges from 2.8 to 5.5 months. Interestingly, the clinical outcomes of sorafenib treatment, including PFS, OS and post-progression survival, are worse in Asia-Pacific cohort than Western populations. It is also interesting to note dose reduction of sorafenib associated with better PFS and OS from the Eastern data. Besides, the baseline clinical characteristics of patients, the prognostic factors and predictors of sorafenib benefit are also different in Western and Eastern populations. In this speech, we will introduce the Taiwan experience of sorafenib among patients with advanced HCC, and compare the similarities and differences between our data and other studies.

Advance in immunotherapy of HCC

肝癌免疫治療之新進展

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Hepatocellular carcinoma (HCC) is no longer considered a cancer with limited option of drug treatment. Apart from multi-targeted kinase inhibitor, recent clinical data on the use of check-point inhibitors indicate that immunotherapy is efficacious and safe in advanced HCC. The overall aim of the lecture is to enhance the understanding of audience on the current status of development of immunotherapy on HCC. In the lecture, the rationale of using immunotherapy in hepatitis virus-related HCC will be discussed. Latest clinical development of immune checkpoint inhibitors will also be presented, with update on the ongoing phase III clinical trials and important phase I/II data. Finally, the challenges on the use of immunotherapy in HCC including biomarker, combinational strategies as well as the potential issue of accelerated progression will be discussed.

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新時代麻醉供氧器材研討會
暨北區麻醉月會

Oxygen Supplement Devices Make Anesthesia Easy and Safe

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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新時代麻醉供氧器材研討會
暨北區麻醉月會
Oxygen Supplement Devices Make Anesthesia Easy and Safe

The application of THRIVE (Transnasal Humidified Rapid Insufflation Ventilator Exchange) on the anesthesia managements in National Taiwan University Hospital

經鼻高流量氧氣溼化治療 THRIVE 在台大醫院的相關運用經驗

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THRIVE (Transnasal Humidified Rapid Insufflation Ventilator Exchange) is a new type respiratory support method, which is also called HFNC (High-Flow Nasal Cannula) Oxygen Therapy. Initially, it was used as a respiratory treatment for prematures with infant respiratory distress syndrome in neonatal intensive care unit. Medical gas is heated and humidified to prevent damage of respiratory mucosa and preserve the mucociliary function to facilitate secretion clearance. The conditioned gas can be delivered to patients in a high flow rates, more than litters per minute, which generates mild positive end-expiratory pressure and a wash-out of the dead space of upper airway. By this way, it may enhance the gas exchange and decrease the work of breathing.

In the anesthesia managements, THRIVE is able to provide a high fraction of inspired oxygen in an open system. During apnea, the application of THRIVE has been proved to enhance the efficiency of apneic oxygenation. In fact, the DAS (Difficult Airway Society) 2015 guidelines for managements of unanticipated difficult Intubation in adults have suggested it to be a technique for preoxygenation and apneic oxygenation.

From 2016, my department began to use THRIVE in the anesthesia managements for surgical procedures, such as non-intubation thoracic surgery and dental treatments for special needs. The increase of oxygen reserve was observed after the application of THRIVE. Our experience in National Taiwan University

Videostylet assisted realtime DLET insertion

電子影像氣管內管探針輔助雙腔氣管內管置放

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One lung ventilation is required in many thoracic surgical procedures such as pulmonary resections, esophagectomy, thoracoscopy, and trauma to the chest. Ventilation of only one lung is usually accomplished with the use of a double-lumen endobronchial tube (DLET). DLETs are produced in left- and right-sided designs, and correct placement is critical to assure proper functioning and ventilation. Placement of a DLET can be challenging because the view though a laryngoscope is frequently obstructed by the tube itself due to its fixed shape, large diameter, and long length. The traditional approach to placement of a left-sided DLET is to place the tip of the tube though the larynx under direct vision, rotate the tube 90° counter clockwise, and then blindly advance the tube into the left mainstem bronchus to a depth of 27-29 cm (using the teeth as a reference). This technique, however, is error prone because placement on the wrong side can occur and the tube is typically placed until resistance is felt, thus the depth may not be optimal. These drawbacks can result in loss of airway maintenance in a critical situation, leading to catastrophic results. Real-time observation of DLET placement using the Disposcope wireless video style shortens the operation time and increases the success rate of DLET placement as compared to the conventional technique of blind placement and confirmation with FOB in patients with uncompromised airways undergoing elective thoracic surgery that require one lung ventilation. Because of the high success rate and accuracy of tube placement, use of the Disposcope may replace the conventional method of DLET placement and shorten procedure time and eliminate the need for FOB confirmation.

Videoscope in airway management

進階呼吸道管理

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Difficulty airway management (DAM) is a major source of claim in perioperative care, for it may result in brain injury or death. It is essential to establish an effective guideline and to find the new tools to improve the DAM. DAM has bothered the anesthesiologists, emergence doctors and intensive doctors for a long period. Moreover, it is hard to predict before procedure. The common used prediction model has moderate predict power only. To improve the airway management needs a comprehensive strategies and training.

Recently, the DAM was decreased significantly, one of the believed improvement issue is the developing and using new intubation apparatus especially video intubation apparatus. Many video assistant intubation devices have been developed and were suggested as the first alternative choice apparatus when the classical intubation was difficulty in many clinical practices. Some of the anesthesiologists have changed their clinical practice from classical intubation blade with direct vision to the video intubation apparatus as the first choice tool.

Video intubation apparatus versus the classical blade intubation has been proved with advantage on providing better superior larynx view (lower Cormack-Lehane score), higher first attempt successful rate, less the oral pharynx injury, lower the esophageal intubation on new hand especially important the video can shear the images to whole intubation team members thus the intubation was transferred from solo show to be a team practice. The team performance also served the supervisor and colleague can see what the trainee see. This not only may improve the training quality and decrease the possibility to damage the oral cavity.

Here I will present the recent development of new video intubation apparatus and the evidence of using video intubation apparatus in clinical.

The truth, solution and strategy of medical dispute

醫療爭議的真相、解決機制與對策

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台灣的醫療糾紛案件成長迅速，平均每七到十位醫師，每年會遭遇一件醫療糾紛，醫療糾紛已經成為醫學生選擇科別的重要考慮因素之一，也實質影響了醫師的醫療行為以及醫病關係。

本演講中，我們將分享我們過去十多年，針對台灣醫療糾紛所進行的實證研究，分別由醫師的主觀面、鑑定報告書及法院判決書的客觀面，剖析台灣醫療糾紛發生的原因、解決的方式、醫師勝敗訴的機會、案件判決的賠償金額或者宣告刑期、探討鑑定報告的重複鑑定率及維持率、判決的上訴率及維持率，等相關實證研究結果。

此外，本演講也將探討台灣醫療爭議案件，衛生福利部推動的醫療爭議處理法草案中，將相關病患關懷機制、多元雙向解決機制、國家救濟制度、以及相關文件賦予法律追溯豁免權等等議題。對於臨床醫護人員或者對於醫療糾紛有興趣的學者，本課程將提供具有代表性的醫療糾紛個案，並有第一手的醫療糾紛實證研究結果分享，會是一堂頗有收獲的課程。

Pain trajectory analysis

疼痛軌跡分析

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Accurate and reliable pain assessments are the fundamental of good postoperative pain control. Traditional pain assessments are difficult to handle the dynamic variablility of postoperative pain. In contrast, trajectory analysis not only provides higher resolution view on the transition process of postoperative pain but also breaks through the limitation of traditional pain assessments to provide new turning points for both clinical care and academic research.

The aims of this speech are introducing how to analyze pain trajectories with statistics methods, examining the association between pain trajectories and surgical outcomes and providing analytical suggestions of pain assessments results for clinicians and researchers.

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2018年榮總台灣聯合大學合作研究
第14期成果發表會

Symposium of VGH-UST Joint Research Program

時 間：107年6月30日　　09:15~12:30

Time：June 30, 2018　　09:15~12:30

地 點：台北國際會議中心 101D 會議室

Place：Conference Room 101D
Taipei International Convention Center

2018年榮總台灣聯合大學合作研究
第14期成果發表會
Symposium of VGH-UST Joint Research Program

The role of iNOS and TPSO-mediated regulation in pathogenesis of PTSD

iNOS 與 TSPO 介導調控創傷後壓力症候群 之病理調控機制

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背景

研究文獻指出，包括創傷症候群在內的情緒失調型精神疾病，多與神經發炎或免疫功能失常有關，早期臨床研究證實抗發炎藥物可降低憂鬱症狀，這項結果促使科學藉開始思考相同形式的治療或可用於其他心理疾病，如創傷症候群。

一般被認知為”抗壓激素”的皮質醇 (cortisol) 在創傷症候群合併重度憂鬱症的病人體內呈現低濃度；而在只有罹患重度憂鬱症的病人體內則測出高濃度。如果是因為早年遭受創傷而致使的重度憂鬱症 (非創傷症候群) 患者體內皮質醇則偏低。研究更指出創傷症候群合併重度憂鬱症的病人體內含有高濃度的發炎指標因子 - inflammatory marker interleukin-6 (IL-6)。

另一方面，在神經發炎過程中，最典型的現象就是微膠細胞的大量聚集與其粒線體外膜上的轉位蛋白 (18-kDa translocator protein, TSPO) 濃度大量上升。在 PTSD 引發的神經炎症中，轉位蛋白的濃度變化被認為極有潛力發展成影像類生物標記 (biomarker)。

方法 本計畫主題為（一）優化分別以 iNOS 與 TSPO 為標的物的 PET 造影劑 -[18F]FBAT 與 [18F]FEPPA 之核醫藥物合成以符合臨床標準並同時研發以誘導型一氧化氮酶為結合標的的 [18F]FBAT，以符合臨床試驗之質量等級。（二）以此新興核醫正子掃描造影劑 [18F]FEPPA 與 [18F]FBAT 併用 PTSD 大鼠進行 30 分鐘 PET ／ CT 動態造影，用以觀察抗發炎藥物治療前後，在各個不同腦區之發炎程度變化。（三）以 RNA 定序法探討杏仁核、前額葉、下視丘的基因表現變化，有解鑑定出涉及 PTSD 的相關基因，以及助瞭所引發的細胞學及組織學變化。

結果

[18F]FEPPA與[18F]FBAT藥物合成品管控制已符合臨床試驗標準。在以lipopolysaccharide (LPS)藥物誘發之急性發炎動物模式中，我們證實[18F]FEPPA與[18F]FBAT分別對TSPO與iNOS的影像特異性；也證實在神經發炎反應中Ｍ1與Ｍ2期間，TSPO與iNOS的前後交替變化。而在創傷症候群大鼠模式中，我們更發現全腦性的發炎現象，尤其在與情緒反應相關之視丘、海馬迴、杏仁核部位。在抗發炎藥物治療後，原發炎區域明顯降低。經由藥物治療後，創傷症候群鼠腦杏仁核與神經退化疾病相關之基因恢復為接近正常狀況，而免疫系統基因則在治療後表現下降。

結論

本研究結果證實[18F]FEPPA適合用於PTSD的核醫影像診斷與預測治療效果。而對於其他神經發炎相關病症，如：阿茲海默症、急性腦挫傷應更進一步探究。

Non-invasive cardiac stimulation using optical and magneticinterventions

光磁遺傳學非侵入心肌刺激模式之探討

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背景

光遺傳學是一種新穎和強大的技術，可以非侵入激活或抑制細胞電力，並有潛力被用作固有 cardioconversion 的替代方法。本計劃旨在探索活體大鼠心臟光遺傳學除顫及起搏方法，並優化光學電路工程需求。大鼠會經由光遺傳基因的 AAV 載體感染。一旦該基因在心臟中確認表達，將會誘發心室纖維性顫動並嘗試經傳遞到心臟的光能量終止心律失常。這是首次嘗試在活體大鼠光遺傳學心室除顫。所建立的經驗和方法對於未來擴展研究將是非常珍貴，甚至可能革新心律疾病的醫療管理方式。

方法

<u>病毒注射及光刺激</u>

小鼠經由頸靜脈注射線相關病毒 (AAV virus)，四到六週後，小鼠吸入氣體麻醉劑及裝上呼吸器，進行開胸手術，持續測量心電圖訊號，利用電刺激器，誘導心室過速及心律不整，再以藍光 LED 連續或間歇照射左心室，觀察心電圖的變化，以及不同強度的藍光對於去除心律不整的效應。

結果

腺相關病毒感染心臟的效率，是本次實驗的主要因素，經由頸靜脈注射不同濃度結果顯示，注射濃度越高，能感染心臟的效率越好，由先前經驗累積，約 10^{11} 次方 vg 以上，感染效率會大幅提升，在單層細胞層次而言，感染的效率有達到五成以上，即可利用藍光 LED 激發離子通道，產生電位改變，打入不同的藍光頻率、強度、脈衝以及深度，對於除顫效果也有十分大的關係，另外就整顆心臟而言，也約略五成以上即可讓心臟動作電位發生改變，達到除顫的效果。

結論

本次研究持續將心臟感染效率的提高，對於自製的線相關病毒的感染力，已達到本次研究的目標。製造高濃度的線相關病毒，也持續開發新的技術，未來在腺相關病毒製造的技術更純熟後，將能取代植入式心臟除顫器，成為未來新的治療方式，能減輕心臟病患者的治療風險。

Comprehensive studies of miR-196a in HCC

系統性探討 miR-196a 在肝細胞癌的角色

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背景

肝癌是台灣成人最重要的癌症之一，其成因與台灣之高 B 型肝炎感染率有密切關係。微型核糖核酸 (MicroRNAs) 為長度只有 18-25 個核苷酸的小型核糖核酸，近來發現與胚胎幹細胞的特性基因之調控有密切關聯。微型核糖核酸近來被認為可能經由調控幹細胞特性基因而活化癌細胞的轉移。我們以前的研究應用次世代定序研究在不同年齡族群帶有 B 型肝炎病毒肝癌患者肝癌組織之微型核糖核酸體中 miR-196a 有差異表現。微型核糖核酸 miR-196a 表現量高的和巨視血管侵犯、非早期肝癌、較高的手術後復發率、較低的無腫留存活追蹤、以 Kaplan-Meier 分析有較高的累積復發率。本計劃將闡明 miR-196a 在肝癌的調控機制、肝癌轉移的分子機轉、與幹細胞特性基因之間的相互關聯性。其結果將對肝癌的預後及治療有重要貢獻。

方法

本研究計畫將評估探討我們將會使用體外肝癌細胞株與小鼠模式探討 miR-196a 調控的生化途徑在肝癌中之致病與轉移機轉。以包含針對 miR-196a 的短髮夾針 RNA 的慢病毒 (lentivirus encoding short hairpin RNA targeting miR-196a) 降調PLC肝癌細胞的miR-196a，以觀察對肝癌細胞聚球、侵犯、穿透血管內皮細胞、小鼠異體移植腫瘤成長與肺部轉移的影響。我們也將以生物資訊學之方式尋找 miR-196a 上下游基因標的，以及相關活化的幹細胞特性基因與轉移相關標的基因，並以體外分析技術確認之。我們進一步構築 以桿狀病毒為載體內含致癌的 miR-196a 和正常組織表現的 miR-126 或針對 miR-196a 的短髮夾針 RNA 轉導肝癌細胞株，以選擇性的將在體送至肝癌細胞。

結果

在第一與第二年的研究，我們發現降調 miR-196a，的確可以改變肝癌細胞株的表現型：如降低聚球與移行能力、穿過內皮細胞的移行能力、減少異體移植的腫瘤大小與肺轉移的結節等。降調 miR-196a 使得 Slug, Twist, Oct4 and Sox2 表現降低，也減少異體移植腫瘤的新生血管生成。

結論

本研究顯示高表現的 miR-196a 和肝癌進行有關。體外和活體研究皆顯示 miR-196a 和腫瘤成長、血管生成與肺部轉移有關。降調 miR-196a 會減少新生血管。同時也發現對在表皮細胞間質化中的 Twist、Slug、Vimentin 也會隨之減少表現。以桿狀病毒為載體內含針對 miR-196a 的短髮夾針 RNA 轉導肝癌細胞株可降低腫瘤成長和血管生成，是有潛力的治療用載體。此研究的發現將對為來發展新穎的有效治療預後不良肝癌的治療模式。

Targeting the dosage for optimal Ketamine level for clinical trial and using wireless frontal EEG as a biomarker to predict response in refractory depression

尋求 K 他命使用於難治型憂鬱症之目標劑量，進行臨床和影像試驗及利用無線腦機之額葉腦波作為生物標記以預測 K 他命之療效

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此整合計畫的目的在 (1) 找尋治療難治型憂鬱症 (TRD) 最適當的 K 他命療效劑量；(2)K 他命在其快速療效時，腦部何處區域之醣類代謝亦同時改變，來解釋 K 他命之快速致療憂鬱症的機轉。(3) 由於腦前額葉與情緒障礙 (憂鬱) 有關，是否利用無線腦機之偵測額葉腦波在 K 他命注射後作為其生物標記來預測 K 他命之療效。研究一：西方之研究以 0.5mg/kg K 他命治療 TRD，發現大約有 65%-70% 為良好反應者 (即原始憂鬱分數下降超過 50% 以上)。而同樣劑量在臺灣之研究其良好反應者卻只 45.6%。我們發現台灣個案的 Ketamine 及 Norketamine 的血中濃度竟然為西方人的一半。爰此，我們收集 6 位 TRD 病患，給予較高劑量 (0.8mg/kg) 之單一注射，我們發現在注射後 240 分鍾之症狀評估，其良好反應率達 66.7%，確實高於先前給予 0.5mg/kg 的 45.6%。Ketamine 和 Norketamine 的血中濃度亦接近西方研究之使用 0.5mg/kg 之血中濃度。然由於我們以 0.8mg/kg 為一開放式研究，且個案僅6位，故需進一步擴大研究樣本及進行隨機雙盲研究，才能加以證實。研究二：以 18F-FDG 正子影像造影在 K 他命注射前及 40 分鐘注射後之比較。發現 K 他命 0.5mg/kg 造成腦前額葉代謝攝取率增加。而相反的，皮質下杏仁核之攝取率卻下降，符合抗憂鬱劑反應之腦部變化的發現。腦前額葉醣類攝取量的增加與憂鬱症狀 (40 分鐘及 240 分鐘) 的改善成正比。更證明 K 他命快速療效的機轉。研究三：基於以上正子造影之發現，以交通大學林教授團隊發明之穿戴式無線腦機偵測腦前額葉腦波之方法。我們發現以下兩種腦波之生物標記可以作為偵測 TRD 病患對 K 他命之療效。其一為良好反應者其在未用 K 他命前，比不良反應者之 Theta 波為弱。其二良好反應者在 K 他命治療前後腦波比較，發現治療後其腦波之 α 波能量變得較強，且 α 波在治療前之左右腦不對稱 (Asymmetry) 的現象，0.5mg/kg K 他命之給予，其左右不對稱之比率下降。這些前額葉腦波之變化，可以作為預測 K 他命療效之生物標記。

結論

此整合型研究提供了臺灣療難治型憂鬱症 (TRD) 病患對少量且單一劑量 K 他命之療效反應達理想境界的劑量調節和 K 他命對腦部區域醣類代謝之快速改變及立即療效的相關機轉。以及以簡單實用之穿戴式腦波儀，即可偵測病患是否對 K 他命有效之生物標記。

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台日幹細胞治療與再生醫學研討會

Frontier iPS and Stem Cell Therapeutic Summit 2018 in Taipei

指導單位：行政院科技部/行政院衛生福利部
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Time：June 30, 2018 08:30~12:10

地 點：台北國際會議中心 102 會議室
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Taipei International Convention Center

台日幹細胞治療與再生醫學研討會
Frontier iPS and Stem Cell Therapeutic Summit 2018 in Taipei

iPS cell derived photoreceptor transplantation

iPS 細胞來源的感光細胞之移植

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iPSC-retina transplantation is a promising treatment to restore visual function to degenerated retinas. The retinal sheet transplantation, which supplies photoreceptors and secondary retinal neurons, has been shown able to reintroduce visual function in mice with end-stage retinal degeneration. Transplanted retina sheets generally survive for a longer period than suspended cells, however, the presence of secondary neurons often becomes a physical hindrance and restrains photoreceptors from making contact with the host secondary neurons. The goal of this study was to introduce a new strategy for iPSC-retina transplantation which overcomes this difficulty while preserving the advantages of retina sheet transplantation.We successfully prepared two KO iPSC lines with a similar in vitro retinal differentiation potency to wildtype cell lines, indicating normal early retinal development. After transplantation, both KO iPSC-retinas readily integrated to the host, with an apparently improved contact judging by the overall proximity of graft photoreceptor cells and host bipolar cells. Importantly, the number of graft ON bipolar cells was drastically decreased in the KO lines. Synaptic contact between graft photoreceptors and host bipolar cells was confirmed by immunohistochemistry. Both MEA recording and two-photon calcium imaging showed that grafted cells could elicit light responses in the host ganglion cells. Genetically engineered iPSC-retina is a viable strategy for preparing retinal sheets for transplantation with fewer secondary neurons. These grafts can readily integrate to the host as the wildtype retinal sheets do, while improving the contact of graft photoreceptors with host bipolar cells.

Recent advances in cell sheet-based regenerative therapy

細胞層片於再生醫學之最新進展

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In addition to stem cell biology, tissue engineering is an essential research field for regenerative therapy. There are several strategies in tissue engineering. Most popular approach is scaffold-based tissue engineering, which utilizes a biodegradable scaffold as alternatives for extracellular matrix. Recently, bioprinting technology has rapidly emerged and shown the possibility of 3-dimensional (3D) tissue fabrication with each cell position control. By contrast, we have developed "cell sheet-based tissue engineering" which utilize cell sheets harvested from temperature-responsive culture dishes. Contiguous intact cell sheets are harvested from the culture dishes only by lowering temperature. Monolayer or stacked cell sheets are transplantable directly onto damaged tissues and cell sheet transplantation therapies have already been clinically applied for cornea, heart, esophagus, cartilage, ear and lung diseases. The technology has been also applied in preclinical experiments for various tissues and organs including liver, kidney, muscle, pancreas, brain, thyroid and uterus. 3D functional tissues are also fabricated by stacking cell sheets. Especially functionally beating cardiac tissues have been successful fabricated. However, the lack of vasculature limits the viable tissue thickness. In cell sheet-based tissue engineering, about 3 layers is limit for layering cardiac cell sheets without vasculature. Therefore, multistep layering of triple-layer cardiac cell sheets co-cultured with endothelial cells has been used to fabricate thick vascularized beating tissue both in vivo and in vitro. Now fabrication of vascularized thick myocardial tube which might have pumping potential is now ongoing. Cell sheet-based tissue engineering has revealed great potential to regenerative therapy and should contribute to future organ engineering.

Synthetic microRNA switch technologies to purify cells and program cell-fate

透過合成小分子核酸調控純化細胞並編程細胞生長途徑

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The precise identification and purification of target cell types is critical to both study cell function and prepare cells for therapeutic applications. Gene delivery using mRNA rather than DNA may be safer owing to a reduced risk of genomic integration. By designing microRNA (miRNA)-responsive mRNAs (miRNA switches), we developed a method for high-resolution identification, separation, and purification of target cell types. We designed mRNAs encoding a protein of interest tagged with complementary sequences of target miRNAs. These miRNA-responsive mRNA switches can control translation of transgenes depending on endogenous miRNA activities and purify variety of target cells, including human ESC/iPSC-derived cardiomyocytes, insulin-producing cells, megakaryocytes, and neurons with high efficiency, accuracy, and safety.

Recently, we prepared a set of "miRNA-responsive, synthetic mRNA library" to rapidly identify active miRNA profiles in each cell type. For example, we newly identified several miRNAs used as specific markers in human naive and primed pluripotent states. Interestingly, miRNA expression levels analyzed by RNA-Seq did not correlate well with miRNA activities analyzed by our library.

Additionally, we developed miRNA-responsive CRISPR-Cas9 system in which the genome editing activity of Cas9 can be repressed (OFF) or activated (ON) through endogenous miRNA signatures, generating "miRNA-Cas9 switch" that selectively edits genome of target cells. Possible applications using these RNA switches will be discussed.

Towards iPSC technology-based regenerative therapy for kidney diseases and diabetes

以 iPSC 技術為基礎腎臟疾病和糖尿病再生醫學治療

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Kidney diseases and diabetes cause both medical and medicoeconomical problems worldwide. Kidney, whole pancreas and pancreatic islet transplantations are an effective therapeutic strategy, but the insufficient donor organ/tissue supply is a major obstacle to these interventions. Regenerative medicine strategies using human induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs) are among the candidate approaches to solve the problems. Based on the knowledge of developmental biology, we are currently developing the stepwise differentiation methods for kidney and pancreatic lineage cells from human iPSCs/ESCs. In addition to conventional treatments using growth factors and cytokines, chemical biology approaches have been introduced to identify novel differentiation-inducing factors by performing high-throughput screening (HTS) of low-molecular-weight chemical compounds. We are also examining the therapeutic potential of kidney and pancreatic lineage cells generated from human iPSCs/ESCs by transplantation into mouse models of renal diseases and diabetes. We have demonstrated that the transplantation of human iPSC-derived renal progenitors ameliorates acute kidney injury (AKI) in mice induced by ischemia/reperfusion injury. We have also succeeded in lowing blood glucose levels in diabetic mice by transplanting human iPSC-derived pancreatic cells. However, the methods to generate kidney and pancreatic lineage cells from human iPSCs/ESCs have not yet been fully established. Further elucidation of the developmental mechanisms and establishing the efficient differentiation methods from human iPSCs/ESCs into the two organ lineages will be required for the development of regenerative medicine strategies. In this presentation, I would like to summarize the current status of kidney and pancreatic regeneration researches using human iPSCs/ESCs including our results and discuss the future perspective of iPSC technology-based regenerative treatment of kidney diseases and diabetes.

HLA homozygous iPS cell stock project for regenerative medicine

再生醫學 HLA 純合子 iPS 細胞儲存計畫

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Ten years have passed since the first report of human iPSCs. The decade has seen much progress in regenerative medicine field, not only basic and clinical science but also in regulation, manufacturing and commercialization. Here, I will introduce CiRA's activity in the "HLA-homozygous iPS cell stock"project, a national-grant-supported project that aims to establish a HLA-typed clinical iPS cell bank for regenerative medicine that covers most of the Japanese population from the aspect of HLA restriction. In the symposium, I will discuss the concept, quality assurances of the production and products, current status, distribution, and future prospection of the iPS bank as an important resource for connecting academic activity and commercialization of regenerative medicine.

Development of cellular reprogramming and iPSC technology as retinal disease-based platform: From bench to clinic bedside

利用生醫電子模式與幹細胞重建視力功能

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The development of induced pluripotent stem cells (iPSCs) has opened a new era for stem cell research. How to quickly, efficiently, and safely produce specific-lineage differentiation from pluripotent-state cells and iPSCs is still an open question. To overcome this critical obstacle, we performed proteomic analysis to find that Parp1, a key factor for DNA repair, plays a crucial role in regulating the efficiency of cellular reprogramming. Furthermore, the generation of patient- or disease-specific iPSCs therefore holds promising potential for the drug industry and regenerative medicine. Following this concept with using iPSC technology, we have reprogrammed T cells from patients with dry type aged macular degeneration (AMD) into induced pluripotent stem cells (iPSCs) via integration-free episomal vectors and differentiated them into RPE cells that were used as an expandable platform for investigating pathogenesis of the AMD and in-vitro drug screening. Moreover, we demonstrated a plasma treated and laminin coated PDMS film that can enhance the attachment, sustain the survival, and facilitate the functional maturation of iPSC-differentiated retinal pigment epithelial cells (dRPE) seeded on it. The dRPE/PDMS-PmL implant was able to enhance the response to light stimuli in vivo. Taken together, our findings provide the pre-clinical examinations for the prospective clinical application of Human iPSCs, including dRPE/PDMS-PmL subretinal implant, in treating aging degeneration diseases like AMD.

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數位病理的發展和應用

Development and Applications of Digital Pathology

主辦單位：中華醫學會
協辦單位：台灣病理學會

時　間：107年6月30日　　08:30~12:20
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地　點：台北國際會議中心 103 會議室
Place：Conference Room 103
Taipei International Convention Center

數位病理的發展和應用

Development and Applications of Digital Pathology

Implementation of digital whole slide system

數位玻片系統之導入

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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 introducing the development of digital pathology, discuss the pros and cons of transforming primary diagnosis using traditional microscopic diagnosis into digital whole slide images, share our experience and considerations in planning for the implementation of digital whole slide system and the AI application developing in our department. Finally, we hope all attendant can find the best way and process to their future digital pathology practice.

Introduction of digital pathology, WSI

數位病理之全玻片影像簡介

Fumiya Fujii

Digital Pathology Business, Business Promotion Department, Systems Division, Hamamatsu Photonics K.K.
Shizuoka, Japan

Digital Pathology is introduced more than a decade, still evolving and adding values as a powerful tool. History of Whole Slide Imaging with some technology, benefit for users, current discussion/matters in practical and future prospect are addressed in the presentation.

Computer aided pathology image processing and its standardized specification

電腦輔助病理影像處理、標記及報告系統之 Web 整合標準化規範

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In this section, we report how image processing techniques with artificial intelligence methodologies can be used to assist pathology image analyses. We performed computer-aided assessment of the Ki67 proliferative index in neuroendocrine tumors. Ki67 proliferative index is defined as the percentage of neoplastic cells immunolabeling for the Ki67 proliferation marker. By performing proper synaptophysin thresholding, hole filling, masking, feature extraction, pre-trained classification, LoG filtering, local maximum intensity determination, we are able to properly count and label the targeted cells. Results of the proposed method are compared with the conventional eye-balling and/or manual counting approaches.

Recently, Digital Imaging and Communications in Medicine (DICOM) standard has addressed a web-based standard (DICOMweb) for the integration of medical image systems. Health Level 7 (HL7) also has announced a web-based standard (HL7 FHIR) for the integration of systems used in clinical healthcare process. Based on these standards, this presentation introduces a web integration framework for data sharing in pathology image examination workflow. The hospital information system (HIS), microscope slide scanner, clinical pathologic web service center and repository, virtual slide viewing and annotation system, and pathology report system could be integrated in the framework. Due to their huge size of virtual slide data, it is not appropriate to encapsulate these virtual slides into traditional DICOM object, to share with DICOM protocols, and to display them in traditional DICOM viewer. We proposed a web solution to handle digital pathology image integration that allows users to share information based on DICOM web and HL7 FHIR protocols.

Toward the future of AI-Driven digital pathology

病理數位轉型所面臨之挑戰與機會

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雲象科技

Research on medical image AI has been blooming in the past few years. Compared with all the glamour it garnered, the process of making of AI is nothing exciting. Behind the scene, there were heroic manual efforts involved in every aspect of AI research, from data collection, pre-processing, annotation, neural network design to hyperparameter tuning. The staggering amount of manual effort required to create AI hints at one crucial factor for sustaining AI research and development: infrastructure. This is especially true for medical image AI. Existing IT infrastructure is outdated for AI research. For example, interconnections between databases are loose or even absent, making retrieval of heterogeneous data within a hospital nearly impossible. Existing formats of diagnostic report are often not conducive to training neural network. As a result, repeat effort of annotation is required. Furthermore, computer servers in a hospital are mostly used for archiving but not computing purposes. This is especially problematic for images with very high resolution such as digital slides. Luckily for digital pathology, which is still in its infancy, some of these problems have not existed yet as systems are just beginning to be built. We envision a future where AI plays important roles in many aspects of digital pathology, from image recognition, decision support to prognosis prediction. The issues currently encountered with medical image AI research would guide us to design robust but flexible hardware and software frameworks for digital pathology critical to the realization of this future. In this talk, we will share some of our results on medical image AI research and our efforts in improving the infrastructure toward the future of AI-driven digital pathology.

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檢驗醫學未來發展趨勢研討會

Seminar on Future Trends in Laboratory Medicine

主辦單位：中華醫學會
合辦單位：台灣臨床病理檢驗醫學會

時　間：107年6月30日　13:30-17:30
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Place：Conference Room 103
Taipei International Convention Center

檢驗醫學未來發展趨勢研討會
Seminar on Future Trends in Laboratory Medicine

Clinical specimens applied for cancer precision medicine: From tissue biopsy to liquid biopsy

臨床檢體於腫瘤精準醫學之應用：從病理切片到液態切片

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Cancer Precision Medicine is a promising and evolving approach that attempts to classify patients with the same clinical diagnosis into different molecular subtypes and tailor their treatment based on genetic mutations found in patients' tumor. The advancement of identification of driver mutations and development of target therapies has made Non-small Cell Lung Cancer (NSCLC) a success story in the era of Cancer Precision Medicine. Given that several oncogenic driver mutations including *EGFR* mutation, *ALK* and *ROS1* rearrangements, etc., serve as therapeutic targets in NSCLC, molecular testing of tumor genetics has become a standard of clinical practice. Although formalin-fixed paraffin embedded tissue (FFPE) obtained from surgical resections or tissue biopsy is the gold standard of sample types for molecular diagnosis, there are some limitations for clinical practice especially in patients with advanced and unresectable tumors. Liquid biopsy using circulating cell free DNA (cfDNA), circulating tumor cells (CTCs) and exosomes has emerged as a non-invasive approach to address tumor genetic alterations, and has potential advantages in cancer early diagnosis, treatment response assessment, progression monitoring and prognosis prediction. In our preliminary study, we found that prior to treatment, the concordance rate of cfDNA and tissue biopsy toward *EGFR* mutation detection in NSCLC patients was 77.7% (N=115). After EGFR-TKI treatment, the original mutations disappeared in most of patients but usually reappeared before or at the time of clinical progression. Moreover, through cooperation with Prof. Chang, Ying Chih, our study showed that the number of CTCs was significantly associated with tumor stage in NSCLC patients. Our results also strengthen the potential roles of liquid biopsy in Cancer Precision Medicine.

Laboratory automation design experience sharing

檢驗室自動化設計經驗分享

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Laboratory automation has always been the goal of hospital management, patients, laboratory technologists, Laboratory doctors, and clinical healthcare professionals.

1. The principle of laboratory automation:
   (1) It should be started from a simple and easy-to-automate service site (OPD, Emergency, or Hospitalization).
   (2) The automatic transmission of specimens should be designed from the place where the specimen was generated.
   (3) The specimens automatically enter into the analysis system after entering the specimen conveyor system. The whole process is designed as a closed system without human intervention.
2. Service site automation design experience sharing:
   (1) OPD:
      A. Blood:
      Automatic check-in machine, Automatic tube preparation machine, Blood test tube conveyor, Blood test tube collection box, XYZ axis robot arm, Single sample pneumatic tube system, Bulk loader, Automatic centrifuge, Automatic analyzer, Automatic storage test tube refrigerator.
      B. Urine:
      Automatic check-in machine with automatic urine test tube preparation machine, Receiving urine specimen window in toilet (male, female, and handicapped), Urine test tube delivery track, Urine test tube concentration area, XY axis robotic arm, Urine tube automatically inserted into the specimen rack.

(2) Emergency:

A. Blood:

(A) Patient draw blood at emergency blood draw room:

Automatic tube preparation machine, Blood test tube conveyor, Blood test tube collection box, Single sample pneumatic tube system, Bulk loader, Automatic centrifuge, Automatic analyzer, Automatic storage test tube refrigerator.

(B) Patient draw blood at emergency care station:

Blood test tube conveyor belt, Blood test tube collection box, Single sample pneumatic tube system, Bulk loader, Automatic centrifuge, Automatic analyzer, Automatic storage test tube refrigerator.

(3) Hospitalization:

A. Blood:

Blood test tube collection box, Single sample pneumatic tube system, Bulk loader, Automatic centrifuge, Automatic analyzer, Automatic storage test tube refrigerator.

Optimization of the bacterial blood culture procedures

細菌血液培養流程之優化

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Bacteremia is a critical illness that requires quick diagnosis as well as timely and proper antimicrobial treatment. Studies have demonstrated that delayed diagnosis and inappropriate antimicrobial treatment result in prolonged use of antimicrobial agents and higher mortality rate. To expedite the blood culture reports and to quicken the bacterial identification, it is crucial to optimize the blood culture procedures.

Traditional blood culture procedures can be divided into pre-analytic, analytic, and post-analytic stages. Pre-analytic procedures include ordering, blood drawing, transportation, and sign-in. Each step should be monitored to facilitate the transportation time. Traditional analytic procedures include incubation, subculture for the positive samples, identification, and anti-microbial susceptibility tests. Each step is limited by the growth characteristics of the pathogens and their biochemical reactions that differentiate different bacterial species. The performance of the post-analytic reporting system in different hospitals usually depends on the powerfulness of their information department.

Through the help of our information department and others, we have improved our species identification time, shortened the transportation time from the Emergency Department, and the overall blood culture turn around time. To achieve the goals, we relocated a fully automated blood culture machine (VirtuO) in the Emergency Department and used matrix-assisted laser desorption/ionization time-of-fly (MALDI-TOF) spectrometry to shorten the identification. In addition, we established a laboratory information system (LIS) to automatically release positive culture results to the physicians timely. We will share our experience in the coming talk.

The application of LC/MASS/MASS on monitoring serum voriconazole level

應用串聯式質譜儀監測黴飛藥物血中濃度

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Voriconazole is a triazole antifungal drug developed for the treatment of fungal infection. The potent pathogens are including a broad spectrum of clinically significant pathogens, including *Aspergillus*, *Candida*, *Cryptococcus*, *Fusarium*, and *Scedosporium*. The drug inhibits the fungal enzyme 14a-sterol demethylase, a critical step in ergosterol biosynthesis. Voriconazole serum concentrations are difficult to predict because of its saturable metabolism, non-linear pharmacokinetics, and poor correlation to weight-based dosing. For this reason, voriconazole therapeutic drug monitoring may improve efficacy and safety.

In vitro, the voriconazole MIC for most fungi is 0.5-1 mg/L. Because 50% of voriconazole is protein bound (and thus pharmacologically inactive), it makes intuitive sense that a goal serum trough level should be at least 1-2 mg/L. A trough level above 5-6 mg/L is associated with a higher incidence of hepatic and neurological toxicities. Voriconazole levels should be drawn 12 hours after the last dose after the patient has received at least 5-7 days of consistent voriconazole therapy.

Monitoring trough levels of voriconazole is suggested in individuals with reduced liver function, individuals with CYP2C19 polymorphisms associated with poor metabolic function, patients taking other medications that affect CYP2C19 activity, and in patients experiencing potential toxicity. Antifungal TDM is potentially expensive and time consuming, and the ultimate impact on clinical care may be difficult to estimate. Several methods have been used for measuring serum concentrations of antifungal agents, including bioassay, HPLC and mass spectrometry. The current literature shares the experience of the application of LC/MASS/MASS on monitoring serum Voriconazole level in MacKay Memorial Hospital.

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精準醫療於遺傳性疾病

Precision Medicine in Genetic Disease

時　間：107年6月30日　　　08:30~17:30

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Taipei International Convention Center

精準醫療於遺傳性疾病

Precision Medicine in Genetic Disease

Full genome analysis for genetic disease diagnosis

全面分析基因組來診斷遺傳病

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Next-generation sequencing (NGS) has revolutionized the diagnosis of genetic disorders but the causal mutations in many cases are not found readily. One reason for the low yield is that NGS does not produce a fully assembled genome so most structural variations are not detected. Furthermore, some unique sequences found in populations around the world are not part of the reference genome sequence against which the NGS data are compared.

We have developed a strategy to identify, in one set of experiments, all structural variations and single base variants in a patient's genome in a trio study design that we named "full genome analysis" to survey the genome comprehensively. This approach combines long-read DNA sequencing with long single molecule mapping of the genome to produce phased (haplotype-resolved) genome assemblies where structural variations can be identified with breakpoints at single basepair resolution while all genes are covered evenly for single basepair variation detection. Early experience of this approach shows that a significant fraction of the negative NGS cases can be diagnosed by the "full genome analysis" strategy.

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. 2017, total of 1,152,221 newborns have been screened. The incidence of Fabry mutation in male infant is 1/1,397. More than 1,975 individuals carrying Fabry (GLA) mutation were identified at our center. Around 84% (1,648) of them are caused by a specific mutation, IVS4+919G>A. 620 IVS4 adults had undergone echocardiogram for the analysis of the prevalence of left ventricular hypertrophy (LVH) and 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 occurred much earlier than our previous expectation. To achieve a better outcome of Fabry cardiomyopathy, the ERT should be considered to start earlier than current guideline suggested. These findings also highlight the importance of newborn screening for early detection of the insidious but ongoing irreversible cardiac damage in the patients with late-onset Fabry disease.

Advanced therapy of Fabry disease

法布瑞氏症診治新進展

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Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the GLA gene leading to deficient α-galactosidase A activity, glycosphingolipid accumulation, and life-threatening complications. Phenotypes vary from the "classic" phenotype, with pediatric onset and multi-organ involvement, to a later-onset, predominantly cardiac phenotype.

α-Gal A activity testing alone is diagnostic for male patients; however, confirmation of the disease-causing GLA mutation is important to help establish the disease phenotype, rule out benign polymorphisms that cause reduced levels of α-Gal A activity, and it permits the testing of at-risk family members. In female patients, demonstration of the presence of a disease-causing mutation in the GLA gene is required as the plasma enzyme activity is often found within the normal range, although leukocyte α-Gal A activity may be low. X chromosome inactivation studies seems a useful predictor of the global disease severity in heterozygous females.

Care should include ERT or chaperone and adjunctive therapies to treat symptoms that arise due to tissue injury and prevent non-specific progression of tissue injury. Treatment and follow-up assessments to evaluate treatment responses should ideally be supervised by a physician experienced in the management of patients with Fabry disease, with input from sub-specialists who also have Fabry disease experience, as part of a multidisciplinary clinical team that includes a neurologist, nephrologist, cardiologist, medical geneticist, genetic counselor, psychologist, and nurse.

Pedigree drawing and clinical and genetic screening of the at-risk family members of newly diagnosed patients is of critical importance, as additional family members with Fabry disease may be identified from each individual index patient. Screening protocols in high-risk populations are useful in identifying unknown patients and reducing diagnostic delays. However, misinterpretation of screening results may lead to the incorrect assessment of individuals harbouring a non-pathogenic variant in GLA or a likely benign variant and so to the inappropriate initiation of ERT or chaperone therapy. Individuals identified through screening protocols should therefore benefit from careful investigation and an unambiguous diagnosis of FD before any initiation of ERT or chaperone therapy.

Management of adult patients depends on 1) a personalized approach to care, reflecting the natural history of the specific disease phenotype; 2) comprehensive evaluation of disease involvement prior to ERT initiation; 3) early ERT initiation; 4) thorough routine monitoring for evidence of organ involvement in non-classic asymptomatic patients and response to therapy in treated patients; 5) use of adjuvant treatments for specific disease manifestations; and 6) management by an experienced multidisciplinary team.

Very early treatment for Pompe disease contribute to better outcomes: 10-year experience of in Taiwan

非常早期酵素補充療法於龐貝氏症：台灣之十年經驗

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Background Newborn screening is the only way to initiate the very early diagnosis and treatment. Our team at the Taipei Veterans General Hospital (TVGH) began Pompe newborn screening from 2008, testing approximately two-thirds of the newborn population in Taiwan. Until now, it is more than one million newborns who were transferred for confirming diagnosis to our hospital. By 2010, we had established an effective newborn screening program with rapid diagnostic strategies, and almost all of the suspected IOPD infants could be diagnosed correctly and receive first time ERT within 4 hours of admission. With such an effective system, the average age of our IOPD patients started their ERT at about 9.6 days of age, the earliest group all over the world. To evaluate whether very early treatment in our IOPD patients would result in better clinical outcomes, comparing these data to our LOPD patients who were diagnosed by clinical evaluation before NBS program started and other IOPD study groups. This is a ten-year cohort study.

Methods We diagnosed 26 IOPD, suspected LOPD in 48 of these newborns. Five LOPD patients diagnosed by clinical evaluation before NBS program started and were treated in our hospital.

Results After 2010, the mean age at first enzyme-replacement therapy (ERT) for our IOPD patients was 9.6- day-old. Our patients had better biological, physical, and developmental outcomes and lower anti-rh acid α-glucosidase antibodies after 2 years of treatment, even compared with one group that began ERT just 10 days later than our cohort. No our IOPD patient needed invasive ventilation support. The mean age for independent walking was 11.6 ± 1.3 months, the same age as normal children. Furthermore, comparing to the LOPD patients who were diagnosed by clinical evaluation and the age of conforming diagnosis were around 12-yaer-old, our IOPD patients who had more severe form of this disease have better clinical outcomes.

Conclusion ERT for patients with IOPD and LOPD should be initiated as early as possible, before irreversible damage occurs. Our results indicate that early identification of patients with Pompe disease allows for the very early initiation of ERT. Starting ERT even a few days earlier might lead to better outcomes.

Phenotype-genotype correlations in Pompe disease

龐貝氏症的基因型與其臨床表徵之關聯性

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Pompe disease is inherited as an autosomal recessive trait. It is an lysosomal glycogen storage disorder which is caused by mutations in the gene encoding acid α-glucosidase (GAA). Thus enzyme deficiency results from different mutations in the GAA–gene.

The correlation between genotypes and phenotypes is clear in so far that patients presenting with the most severe phenotype, classic infantile Pompe disease, have two pathogenic mutations. Necessarily the mutation have to be located in each GAA allele. These mutations cause the lowest levels or nearly no enzyme levels. All patients with less progressive phenotypes have at least one sequence variation that allows normal or low level synthesis of GAA leading to the formation of analytically measurable, low level GAA activity in most cases.

In the last years it became obvious that patients with late onset of Pompe disease (LOPD) exhibit higher levels of GAA enzyme and therefore suffering from a much milder form of the disorder. It is known in the meanwhile that the correspondence between the genotype, remaining enzyme activity and clinical phenotype is most likely genetically based. On the other hand there are some mutations as the for example the c.-32-13C>T mutation in which the phenotype is much more variable than with other mutations. This observation leads to the conclusion that modifying factors may play an important role in the phenotypic expression. These modifying factors will be addressed in future studies. The better understanding of these factor will also help to better understand possible further therapeutic approaches in addition to enzyme replacement therapy (ERT).

Fabry disease: Characterization of the plasma proteome pre and post enzyme replacement therapy

酵素替代療法對法布瑞氏症在蛋白質體學上的特徵變化

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Fabry disease is characterized by the progressive accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids in vascular endothelial cells. Enzyme replacement therapy (ERT) clears this accumulation. We analyzed plasma proteome profiles before and after ERT to characterize its molecular pathology.

Two-dimensional electrophoresis and matrix-assisted laser desorption/ionization-time of flight tandem mass spectrometry (MS) and MS/MS were done using plasma samples before and after ERT in eight patients with classical Fabry disease

After short-term ERT (4–12 months), the levels of 15 plasma proteins involved in inflammation, oxidative and ischemic injury, or complement activation were reduced significantly. Among them, beta-actin (ACTB), inactivated complement C3b (iC3b), and C4B were elevated significantly in pre- ERT Fabry disease plasma compared with control plasma. After longer-term ERT (46-96 months), iC3b levels gradually decreased, whereas the levels of other proteins varied. The gradual reduction of iC3b was comparable to that of Gb3 levels. In addition, iC3b increased significantly in pre ERT Fabry disease mouse plasma, and C3 deposits were notable in renal tissues of pre-enzyme replacement therapy patients.

These results indicated that C3-mediated complement activation might be altered in Fabry disease and enzyme replacement therapy might promote its stabilization

Inflammation and Fibrosis: Understanding implications of immune system activation on disease progression

發炎和纖維化：免疫系統活化對法布瑞氏症疾病進展的影響

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Inflammatory renal pathologies may start with a direct interaction between an external molecule (e.g. an antigen fragment) and a cellular receptor, such as a Toll-like receptor (TLR), and direct activation of the complement cascade. These innate immune responses activate circulating monocytes and resident glomerular cells to release inflammatory cytokines and result in the activation of the adaptive immune response. Inflammatory processes can be self–limiting; alternatively, therapy can reduce or stop pathological processes with "restitution ad integrum" of the tissue. When inflammatory processes last over time, the production of cytokines by inflammatory cells results in fibrosis. These cytokines (e.g. transforming growth factor [TGF]-beta) can increase the synthesis of pro-fibrotic molecules, like collagen, or drive the de-differentiation of parenchymal cells that acquire the capacity to synthesise molecules determining fibrosis. The final result is fibrosis and sclerosis of tissue.

In Fabry disease, it was demonstrated that Gb3 deposition might interfere with lysosomal functions, not only in the catabolism of many substances but also in immune function. Indeed in the lysosome, the composition between antigen and the major histo-compatibility complex (MHC) occurs just before presentation to dendritic cells. This lysosomal change may over-stimulate an aberrant immunological response with activation of innate immunity via TLR4. TLR4 receptors are present in glomerular and epithelial cells and may activate the innate immune response, resulting in long-lasting inflammation supported by the production of pro-fibrotic cytokines. Proteinuria itself can activate tubular epithelial cells and transform them into different kind of cells (e.g. mesenchymal cells) through activation of TGF-beta and other pro-fibrotic molecules. Also, it has been demonstrated that Gb3 may interact with molecules like Notch 1, which stimulate synthesis of TGF-beta, producing tissue fibrosis. Following inflammatory processes in the kidney, urine from Fabry patients has been shown to contain high levels of cytokines, which go back to low levels after treatment with enzyme replacement therapy.

Therefore, it is possible to speculate that the deposition of Gb3 in all kinds of cells starts a chain of events driven by lysosomal alterations, involving the immune system (innate immunity) and resulting in organ damage. From this point of view, a prompt start of enzyme replacement therapy is suggested, because, at least in theory, when inflammation processes are triggered, they can proceed to fibrosis independently from the cellular clearance of Gb3

Expanding the newborn screening program in the Philippines

菲律賓擴大新生兒篩檢

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Newborn screening is an important public health intervention historically proven worldwide to significantly lower infant morbidity and mortality with the early identification and management of affected newborns. Newborn screening started in the Philippines in 1996 with a basic panel of congenital conditions including CH, CAH, Gal, PKU, and HCY. By 2000, HCY was replaced by G6PD def due to a lack of case finding and in 2012, MSUD was added. Preparations for expanded newborn screening (eNBS) led eventually to its offering by December 2014. Critical to the decision was data from the California USA newborn screening program that revealed a significant number of Filipino newborns with confirmed cases of the expanded disorders. This prompted the Department of Health (DOH) National Technical Working Group on Newborn Screening to support its offering as a choice for the family – basic panel of 6 conditions covered by insurance vs eNBS of 28 conditions with additional cost paid by the family. The 28 include organic acidurias, amino acidurias, cystic fibrosis, hemoglobinopathies, biotinidase deficiency.

The Newborn Screening Act of 2004 (Republic Act of 9288) provides the framework for implementation of the program with the DOH as the lead agency. Every newborn must be given the opportunity to be screened. The newborn screening laboratories are geographically located, with each expected to screen at least 50,000 – 300,000 newborns annually. Currently, there are 6 laboratories to cover 2.2 M babies, which is 70% screening coverage for the basic panel and 16% covered for eNBS. As the program pushes for 100% coverage, 3 more laboratories are being prepared. Regional continuity clinics have been developed primarily for the long term follow-up of positive cases. The Rare Disease Act of 2016 (Republic Act of 10747) complements the Newborn Screening Law in further supporting the patients with rare conditions.

This March 2018, the Philippine Health Insurance Corporation approved the funding of eNBS for all its members, bringing a major challenge to its infrastructure. All laboratories are currently upgrading their facilities to meet the screening demands as we transition to full implementation of eNBS.

Continuing and emerging challenges will be discussed.

Challenge for diagnosis and treatment for Krabbe disease including the experience of BMT on LSD in Japan

利用骨髓移植治療溶酶體儲積症 - 克拉伯病 (Krabbe disease) 日本之診斷與治療

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Krabbe disease is an inherited demyelinating disease caused by deficiency of the lysosomal enzyme, galactocerebrosidase. It is recognized as one of the predominant genetic diseases showing leukodystrophy from infancy to adulthood. The clinical phenotype and genotype for this disease show considerable variation worldwide, which makes accurate diagnosis difficult. Effective therapy is limited, although hematopoietic stem cell transplantation at an early stage has been established to some extent.

I report about genotype-phenotype correlation for the possibility of early diagnosis at pre-symptomatic stage. Moreover I mention about the experience of hematopoietic stem cell transplantation for the patients of Krabbe disease including other lysosomal diseases in Japan. In Japan we have experience for hematopoietic stem cell transplantation for more than 150 patients of lysosomal disease in last 25 years including seven Krabbe patients.

In the near future, newborn screening for several lysosomal diseases might be considered and make contribution on the better life for for the patients.

Current studies of mucopolysaccharidosis 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

台灣脊髓肌肉萎縮症之新生兒篩檢及治療經驗

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鐘育志

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Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder characterized by motor neuron dysfunction resulting generalized muscle dysfunction, secondary to the mutations of survival motor neuron 1 (SMN1) gene causing widespread decreased SMN level. SMN2, a SMA modifier gene, is intact in all SMA patients but contains a C-to-T variation in exon 7 that affects a splice enhancer and determines exclusion of exon 7 in the majority of its transcript, leading to an unstable protein that cannot compensate for full-length SMN protein. To date, SMA is the leading genetic cause of infant mortality in the world.

In 2007, a consensus statement on SMA standard of care (SOC), has been widely used throughout the world. Those SOC recommendations have been revised in 2018 to cover 8 care areas: diagnostic and genetic counseling, pulmonary, acute care management in the hospital setting, orthopedic (spinal curvature, joint contractures, fractures), physical therapy and rehabilitation, gastrointestinal and nutrition, other organ systems involved in SMA, ethical considerations and palliative care.

In the past decade multidisciplinary investigators have identified different SMN-dependent therapeutic approaches including SMN2 ISS-N1 targeting antisense oligonucleotides, SMN2 targeting small molecules, and gene therapy that show promise in treating SMA. Until recently FDA has approved nusinersen,the first treatment drug for children and adults with SMA in US (December, 2016). However, careful analysis of SMA animal models and patients has revealed some limitations that need to be taken very seriously, including a limited time-window for successful therapy delivery, making newborn screening (NBS) of SMA mandatory.

In this presentation, we will outline the most updated therapeutic strategies and NBS that are currently developing, which are represented by multidisciplinary ways for the treatment and a changing landscape in SMA new therapeutic era.

Flagship program of precision medicine in Taiwan: What have we learned from rare genetic disorders?

台灣精準醫療旗艦計畫：從遺傳性罕見疾病之研究中，我們可以學到什麼？

<u>Shih-Feng Tsai</u>, Yung-Feng Lin

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Most rare diseases are genetic and appear early in life. A large number of them are not well characterized or genetically undefined. Whole-genome sequencing (WGS) has been shown to be an effective tool for investigating patients with Mendelian diseases. To help clinicians manage the patients with undiagnosed disease, we have established the Taiwan Rare Disease Network (TRDN) to recruit patients with undiagnosed, genetic or severe diseases, and we have sequenced their DNA by using the Illumina NovaSeq 6000 sequencers. In 2017 Q4, we studied 18 families from six hospitals. To date, we have completed the analysis on nine families by WGS analysis and identified the causal mutations in seven. Among them, a three and half years old boy was referred to have genetic analysis for his multiple developmental defects, including hypotonia, eye abnormalities of microphthalmos, enophthalmos and strasbismus, and bilateral hearing impairment. We conducted WGS on the patient and his parents, who otherwise have normal auditory and visual functions. After trimming off low-quality reads, the shotgun short sequences were mapped to the human reference genome (hg19). Private variants were examined for nonsynnymous changes that might impact protein functions. By comparing to the disease-associated databases, we selected candidate genes for validation based on the inheritance pattern. Mutations in two genes: CDH23 (Asn149fs) and MYO7A (Arg1602Gln), were identified, and each was inherited from one of the parents. Thus, the data are consistent with the digenic recessive model of two interacting genes to cause the phenotype or disease. With the single-base insertion leading to frameshift of CDH23, it fits as a ciliopathy - causing the hearing loss. On the other hand, the MYO7A mutation could explain the hypotonia and strabismus. Finally, low vision as a result of CDH23 mutation on the photoreceptors would cause nystagmus. While homozygous or heterozygous mutations of CDH23 or MYO7A singularly have been reported for Usher syndrome, the genomic data shed light on the “two genes” nature of the disease pathogenesis. Consistent with a previous study in the mice that MYO7A is critical for the development and maintenance of bundle function, our study showed for the first time in human that digenic recessive mutation involving CDH23 and MYO7A could lead to phenotypes of Usher syndrome and that CDH23 and MYO7A function together in a complex essential for determining and maintaining cohesion of the stereocilia of the cochlea, eye and muscle. Finally, updates on focused studies of spinocerebellar ataxia and primary immunodeficiency will be presented at this meeting.

Genomic medicine in Taiwan

基因體醫學在台灣

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Knowledge on the genomics-underpinned human physiology and pathology was accumulated quickly due to the fast advancement of high-throughput genomic technology in recent years. Among all technologies available, the single nucleotide polymorphism microarrays and the next generation sequencing method represented two iconic platforms in the early 21st century. The former was the major driving technology for genome-wide association studies, while the latter can quickly elucidate vast amounts of genomic information for research and clinical purposes.

Genome-wide association studies were powerful approaches for identifying disease-pertinent genes and variants in the absence of prior knowledge regarding the potential culprit genes. Variants across the genome, particularly those known to have higher minor allele frequencies, were evaluated by use of the single nucleotide polymorphism microarrays in diseased and non-diseased persons. Apart from the microarrays, rigorous statistical tests accompanied by visual evaluation tools such as the Manhattan plots and PP-plots were critical for a successful discovery. I will present a genome-wide association study which unveiled three candidate genomic regions associated to the co-occurrence of two primary cancers, the transitional cell carcinoma and hepatocellular carcinoma.

The next generation sequencing, on the other hand, was capable of indicating the causative mutations of familial diseases which often have high-penetrance genetic defects. I will present a case study on Ataxia Telangiectasia, which is an inherited recessive genetic disease where the diseased children harbor two dysfunctional alleles of a gene called ATM. Usually, no obvious symptoms were observed at birth. Using the next generation sequencing, the familial homozygous c.5631_5635delinsA mutation in the ATM gene was found on an index patient who was a 9 year Asian boy. This mutation caused a frameshift of amino acid synthesis and a truncated protein which has a reduced length of 1913 amino acids instead of a normal length of 3056 amino acids. Critical functional domains of the ATM protein such as the FAT, PI3K/PI4K and FACT regions were all missing in this protein. The serum alpha-fetoprotein level was 86 ng/ml and was increased annually. Conventional Sanger sequencing showed that the mutation was inherited from the parents. This boy has a homozygous diseased younger sister and a homozygous normal younger sister.

The prospect of genomics-based human healthcare

基因資訊應用於健康照護之展望

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Since the sequencing of the first human genome in 2003, a tremendous progress has been made towards the technological aspects. With many next generation sequencing (NGS)-based systems, sequencing of individual human genome can now be done in a much lower cost (hundreds of dollars) and a much faster pace (in the same day). In addition, longer read-length of tens of thousands bases from a single stranded DNA has also become available, rendering the determination of large genomic repetitive sequences possible. As the international effort of building data bases containing over a million human sequences of various particular phenotypes is underway, personal genomics era has thus arrived.

Many complex diseases result from interactions between environmental elements and genetic factors. The association of genetic polymorphisms and susceptibility to diseases is establishing a new paradigm for the understanding of personal genetic risk factors. Genetic variations also correlated with efficacy of drugs for patients. Stratifying the etiology of disease in groups of patients based on genetic differences sets the stage for the development of pharmacogenomics, which would lead to future personalized medicine. Large scale studies on personal genetic information with various genomic tools have been providing comprehensive solutions that lead to the ultimate goals of medicine: prediction, prevention and personalized protection.

On practical applications, U.S. FDA (Food & Drug Administration) has recently passed a handful of companion genetic tests. For example, the one approved in November 2017, FoundationOne CDx, contains a panel of 8 gene loci which can match against 17 targeted-therapy drugs for the treatment of 5 different cancers. From the insurance payment side, U.S. CMS (Centers for Medicare & Medicaid Services) in March 2018 also started coverage for FDA-approved NGS genetic tests when treating certain types of cancers. Furthermore, in April, 2018 FDA issued a suggested guidance for genetic & genomic-based IVD (in vitro diagnosis), describes how publicly accessible databases of human genetic variants can serve as sources of valid scientific evidence to support the clinical validity in FDA's regulatory review.

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美容醫學新進展

Recent Advances in Aesthetic Plastic Surgery

時　間：107年6月30日　　　8:50~12:00

Time：June 30, 2018　　　8:50~12:00

地　點：台北國際會議中心 201F 會議室

Place：Conference Room 201F
Taipei International Convention Center

美容醫學新進展

Recent Advances in Aesthetic Plastic Surgery

Personal experiences in Asian aging upper blepharoplasty

眼瞼手術：老年人上瞼成形術的個人經驗

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Upper blepharoplasty of young people focuses on producing the ideal shape of the eyelids, but in the elderly, while keeping eyelids in harmony with the rest of the face is an important factor to consider. The operative technique for Asian aging upper blepharoplasty should be based on anatomical structures and their relationship. Modifications to the procedure are correlated with the degree of periorbital aging.

We will present our experiences in aging upper blepharoplasty about balanced concept and clinical considerations in indication, limitation, surgical technique, postoperative complaint and complications. For satisfactory results in aging Asian upper blepharoplasty, the harmonization of the position of the upper eyelid and eyebrow is important.

How to prevent pitfalls and manage complications in bone contour surgery

面部輪廓：顏面骨骼輪廓手術如何預防陷阱和處理併發症

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In recent years, awareness of facial contour has reached a new high thanks to the overwhelming dominance of "selfie" and social media. Self-portrait and self-broadcasting have become a daily routine in younger generation, especially those known as "phubbers" or Facebook addicts. Young females will try everything to look more slender, whether it's losing weight or Botox injection. In those patient who has prominent zygoma and square and lower face, bone contour surgery is often regarded as a silver bullet and last resort.

Because of the wide variation of bone morphology and limited surgical field from intra-oral approach, surgeons are prone to make some mistakes, such as adjacent tissue injury and over-resection. We presented our experience on how to prevent those pitfalls and how to manage complications.

Endonasal augmentation rhinoplasty using autologous tissue

使用自體組織於密閉式隆鼻手術

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Most of the Oriental nose need augmentation. The common problems in Oriental nose are short nose, saddle nose, retracted collumella, boxy tip and insufficient nasal tip. Septum cartilage extension, modification of nasal cartilage, collumellar strut and tip grafting are frequent techniques used in Oriental rhinoplasty. We advocate close method incision to do the primary rhinoplasty cases as well as secondary cases to avoid external scar. The results are as good as open method. The advantages of close method incision are, no external scar can be shown and, columellar blood supply can be preserved.

The disadvantages of using artificial implant (such as silicone, Gortex, Medpor) are extrusion, infection and capsular contracture. We also advocate using total autologous tissue in augmentation rhinoplasty, esp. in secondary rhinoplasty. The materials are ear cartilage, septal cartilage, temporal fasia, dermofat and rib cartilage. The advantages of using autologous tissue in augmentation rhinoplasty are free from complications of extrusion, capsular contracture and an artificial nose after operation.

Totally customized 3D augmentation genioplasty without CT simulation assisted

面部輪廓：不需 CT 模擬輔助之三維度客製化的豐頦手術

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Background

Augmentation genioplasty is one of the commen operations of the facial aesthetic surgeries, but the patients' satisfaction rate is not high. Especially for those patients who have moderate to severe micro-genia and/or retro-genia we need to choose the lager implants. They usually complained about the lump-appearance of implant, unnaturally deep labio-mental angle, and/or obvious pre-jowl depression, even by using the ePTFE-coated silicone implant. The percentage of re-operation for those patient was quite high, comparing to the other kind of facial aesthetic surgeries.

Methods

We tried to use the concept of 3D CT customized implant design. We measured several parameters: lip width, distance between marionette lines, distance from teeth root to the lowest margin of chin, and the patients' favored result. Lower gingiva-buccal sulcus incision is our routine approaching way. During operation, we explored the whole area covered the previously mentioned parameters, found the mental nerves exiting from mandible, and tried to cover the whole area, except the exits of mental nerve, by using soft pliable sheets of ePTFE (Gore-Tex) layer by layer. For those patients who wish to have a sharper chin projection, we sometimes combined to use the Chimeric Chin implant at the most caudal part of chin implant. The whole implants were fixed to bone by the titanium micro-screw.

Results

By carefully designing for the every individual patient, the satisfaction rate of augmentation genioplasty by implant is markedly increased. We could achieve a more nature results with shallower labio-mental angel, even by using the implant as thick as 8-9 mm, improve the pre-jowl depression, and smoother demarcation of implant edge. The same high satisfaction rate was also noted in the revision cases.

Conclusion

Chin is the most caudal end of face and has very large variability 3 dimensionally from patient to patient. Fully customized design for each patient by using soft pliable materials such as ePTFE probably is a good method of choice for augmentation genioplasty.

Secondary augmentation mammaplasty, Diagnosis and management

乳房手術：修正性隆乳手術之診斷和處置

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Background

For secondary augmentation mammaplasty is more challenging to get stable result. Ultrasonographic examination is helpful to find out the reasons of unfavourable result before operation. Implant location plane, capsular contracture, implant malposition, implant rupture can be diagnosed before operation. Thus, help doctors to do precise surgical planning and management.

Method

from 2009 to 2017 , 1066 patient received augmentation mammaplasty.

138 patient had previous history of breast implant augmentation before. 42 patients received

fat grafts augmentation before. Preoperative evaluation by sonogram was done. Implant plane change, neosubpectoral plane, capulectomy, capulorrhaphy, capsulotomy can be chosen before operation. Surgical planning is more precise and the result is more predictable.

Results

Transaxillary Endoscopic operation was more difficult to handle the capsule and operation time is longer, while IMF approach is easier to handle the capsule and shorten the operation time. Reoperaion rate is lower via IMF approach.

Conclusion

IMF approach for secondary augmentation mammoplasty is easier to handle capsule, scar and reduce reoperation rate.

Multi-faceted approach to lower body contouring: gluteal augmentation, liposuction, and fat transfer

身體輪廓：下半身輪廓多層面的策略手術 - 臀部增大，抽脂和脂肪轉移

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As a saying goes: “Parents only have to worry about daughter’s height. For everything else, there are plastic surgeons.” While we definitely can’t increase your daughter’s height, at least we can make her look taller. With a better lower body contour, women will appear slender and taller.

We present our experience of lower body contouring, with a multi-faceted approach, which starts with gluteal augmentation. We use Dr. Gonzalez’s XYZ method with intramuscular placement of cohesive gel implants. Due to the differences between Asian and Caucasian/Latin women, we made several major modifications, choosing smaller implants and deeper insertion plane. Meanwhile, we discarded the subfascial plane and buttock lift surgery because of the tendency of hypertrophic scar.

Then we used liposuction over saddle bags, infra-gluteal region, medial and lateral thigh. In some cases, we injected some fat to buttocks, to increase lateral fullness or correct some surface irregularities.

男性健康論壇2018
Men's Health Symposium 2018

協辦單位：台灣泌尿科醫學會、台灣男性學醫學會、
國立陽明大學書田泌尿科學研究中心
台灣性功能障礙諮詢暨訓練委員會

時　間：107年6月30日　12:50-17:30
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Place：Conference Room 101A
Taipei International Convention Center

本活動由：
輝瑞大藥廠股份有限公司、友華生技醫藥股份有限公司、廣百實業有限公司、台灣安斯泰來製藥股份有限公司、新加坡商美納里尼醫藥有限公司台灣分公司、嬌生股份有限公司楊森藥廠　共同贊助

男性健康論壇2018
Men's Health Symposium 2018

Low intensity shock wave treatment for ED, the new wand for old misery?

低強度震波對勃起功能障礙的治療

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Background

Managing patients with erectile dysfunction (ED) who failed to respond to phosphodiesterase type 5 inhibitors (PDE5is) is a challenging task. Recently, low-intensity extracorporeal shockwave therapy (LI-ESWT) was reported to improve ED by inducing neovascularization and enhancing perfusion of the penis. The current study was performed to evaluate the efficacy of LI-ESWT to convert non-responder to responder of PDE5is and determine the important predictors in patients with ED.

Methods

This was an open-label single-arm prospective study. ED patients with an erection hardness score (EHS) ≤ 2 under a maximal dosage of PDE5is were enrolled. Sociodemographic information and detailed medical history were recorded. LI-ESWT treatment consisted of 3,000 shockwaves once weekly (1000 shockwaves to the distal penis, base of penis and corporal bodies at the perineum)(Storz, Duolith SD1 T-Top) for 12 weeks. All patients continued their regular PDE5is use. The EHS and the 5-item version of the International Index of Erectile Function (IIEF-5) were used to evaluate the change in erectile function 1, 3 and 6 months after LI-ESWT. Success of treatment was defined as EHS 3 or greater, which indicated the regaining of an erection sufficient for vaginal penetration.

Results

A total of 65 patients were enrolled. After LI-ESWT treatment, 45 of the 65 patients (69.2%) could achieve an erection hard enough for intercourse (EHS ≥ 3) under PDE5is use at the 1-month follow-up. Initial severity of ED and history of diabetes were the significant predictors of a successful response. 35 of the 59 patients (59.2%) could still maintain EHS ≥ 3 at the 6-month follow-up (missing cases: 6 of 65, 9.2%). In 42 patients with successful response at the 1-month follow-up, 34 patients could maintain their response at the 6-month follow-up (81.0%).

Conclusion

LI-ESWT can serve as a salvage therapy for ED patients who failed to respond to PDE5is. Initial severity of ED and history of diabetes were the main predictors of a successful response. In those who responded to LI-ESWT, a majority of patients could maintain their effect up to 6-months follow-up. Further longer follow-up studies are still needed to eradicate the long-term effect of LI-ESWT in the treatment of ED.

Vasogenic ED and transvascular angiographic management: Effects of pan-pelvic endovascular intervention on erectile function and lower urinary tract symptoms: Results of computed tomographic angiography and 12-month clinical follow-up from the all-comer PERFECT registry

血管性勃起功能障礙及經動脈治療

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Background

Pelvic arterial stenotic disease is an essential cause for both erectile dysfunction and lower urinary tract symptoms (LUTS). We have previously shown that endovascular revascularization of obstructive penile arterial lesions could ameliorate erectile dysfunction. We herein reported the angiographic and 12-month clinical outcomes of “pan-pelvic” endovascular intervention in patients with erectile dysfunction, with or without LUTS, from the all-comer PERFECT registry.

Methods

Patients with erectile dysfunction and obstructive pelvic arterial lesions (unilateral diameter stenosis ≥ 70% or bilateral stenoses ≥ 50%) undergoing “complete” angioplasty and follow-up multi-detector pelvic computed tomographic (CT) angiography were enrolled. The primary endpoints included in-segment binary restenosis (diameter stenosis ≥ 50%) by follow-up pelvic CT angiography at 8 months, sustained clinical success in erectile function (International Index for Erectile Function-5 [IIEF-5] score ≥ 22 or change in IIEF-5 ≥ 4 and without a later decline by ≥ 4) at 12 months, and clinical success in LUTS (change in the International Prostate Symptom Score [IPSS] score ≤ -3) at 12 months.

Results

A total of 182 consecutive patients (mean age 62.6±7.9 years [range, 42-83 years]) with 334 obstructive segmental lesions (1.8 lesions/patient) and an average IIEF-5 score of 9.1 ± 4.4 were enrolled. One hundred and twelve (34%) obstructive lesions were treated with stenting in addition to balloon angioplasty. At 8 months, the CT angiographic binary restenosis occurred in 102 lesions (102/334, 31%) and 76 patients (76/182, 42%). For lesions located in the proximal internal pudendal artery and above, binary restenosis occurred in only 4 of 113 lesions (3.5%), whereas for lesions located in the distal internal pudendal artery

and beyond, binary restenosis occurred in 98 of 221 lesions (44%). Sustained clinical success in erectile function was achieved in 112 (62%) patients at 12 months, with an overall improvement in IIEF-5 of 5.7 $\pm$ 4.7 ($p < 0.001$). Among patients not developing any binary restenosis, 82% (87/106) achieved sustained clinical success in erectile function, whereas for those with binary restenosis, 33% (25/76) achieved sustained improvement in erectile function. Among the 128 (70%) patients with moderate or severe LUTS (IPSS $\geq$ 8), clinical success in LUTS was achieved in 94 (73%) patients at 12 months, with an overall change in IPSS of -7.7 $\pm$ 8.0 ($p < 0.001$). There were no adverse events except two cases with restenosis experiencing transient worsening of erectile function during follow-up.

Conclusion

In this real-world registry, we for the first time demonstrated the feasibility and effectiveness of complete pelvic arterial endovascular revascularization in the amelioration of erectile dysfunction and LUTS. The low restenosis rate (< 4%) for lesions located in the proximal internal pudendal and iliac arteries and the above 80% sustained clinical success rate in patients not developing restenosis are encouraging. However, for lesions located in the distal internal pudendal and penile arteries, the 40-50% restenosis rate remains a hurdle and quests for further refinement of contemporary intervention strategies.

Situational and subjective premature ejaculation: Clinical significant entity?

情境型與主觀型早洩是主要的臨床病症嗎？

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Premature ejaculation (PE) is a common male sexual disorder and traditionally is classified into lifelong PE (present since the onset of sexual life) and acquired PE (developing after a period of normal function and often associated with erectile problem.). Because his classification did not cover all aspects of PE, Waldinger added two new categories: “Natural Variable (Situational) PE” and “Premature-like ejaculatory Dysfunction (Subjective PE)”.

Epidemiology study of general population showed that prevalence of situational PE and subjective PE were 8.5% and 5.1%, respectively, in Turkish men. A Chinese population study reported that distribution of situational PE (44.1%) and subjective PE (24.8%) were higher than those of lifelong PE (12.3%) and acquired PE (18.8%) in men with PE complaint.

Situational PE is not considered a sexual dysfunction but rather a normal variation in sexual performance, characterized by irregular and inconsistent occurrence of early ejaculations. Treatment of these men should consist of reassurance and education that this pattern of ejaculatory response is normal and does not require pharmacotherapy or psychotherapy.

Men with subjective PE report a diminished control over ejaculation but with normal or extended intravaginal ejaculatory latency time (IELT) of 4-20 min. Because the IELT is normal, the condition is not related to a medical or neurobiological disturbance but rather either to a misperception of ejaculatory time or to a feeling inadequacy for female partner to reach orgasm. Treatment for such patients should adopt psychotherapy first. Pharmacotherapy may be considered for subjective PE men who have high distress levels or have no response to psychotherapy. Controlled trials are required to investigate the optimal treatment for subjective PE.

The erectile function in males seeking for infertility treatment

尋求治療的不孕症男性病患的勃起功能分析

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Background

The prevalence of erectile dysfunction is not well evaluated in the patients of male infertility. Because of the diversity of male infertility, sexual function in those patients is complicated. Within the non obstructive azoospermia, Klinefelter syndrome is a unique male infertility group with hypergonadotrophic hypogonadism. In particular, testosterone is critical for various aspects of sexual response, but its role on penile erection in Klinefelter syndrome (KS) patients is debatable. Whether congenital hypogonadism condition in KS will induce erectile dysfunction?

Methods

We retrospectively collected the clinical data of 58 KS patients with non mosaic 47, XXY karyotype. Hormone profile, body mass index, sexual function (IIEF-5, EHS) were followed and investigated.

Results

Body weight, body height and BMI is in normal range, Testosterone level was below normal range (1.53ng/mL). The main problem is infertility, not erectile dysfunction. In group of normal sexual performance, Testosterone level is not related to IIEF-5. The testosterone level is significant lower in worse sexual performance group than normal group. Our results indicate that erectile dysfunction present in KS is not the main problems and also not specifically associated with the underlying hypogonadal state.

Conclusion

Few studies have evaluated the efficacy of testosterone treatment on sexual dysfunction in these subjects. Testosterone replacement was used routinely in those who have significantly lower levels in KS subjective. Testosterone replacement therapy improved sexual desire, intercourse satisfaction, and overall satisfaction scores, but had no effect on erectile function. Further studies are needed to evaluate the efficacy of testosterone substitution in ameliorating the hypoactive sexual desire often reported in subjects with KS.

The challenge of testicular pathology in micro-TESE-ICSI era

顯微取精與試管嬰兒世代的病理診斷挑戰

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Intracytoplasmic injection of sperm (ICSI) and microdissection testicular sperm extraction (mTESE) are the 2 major leaps lead to the modern advancement in treatment for male infertility. Using these 2 methods, specialists of reproductive medicine are able to retrieve few sperm from male patients of NOA due to various etiologies to make them become biological fathers. However, the diagnosis made at testicular biopsy may sometimes be unmatched to the finding at mTESE. The aim of current review is to explore the mechanisms of disagreement of pathological diagnosis and outcome of mTESE. There are 4 mechanisms identified underpinned the disagreement. Firstly, the sampling bias: the diagnosis made may vary if different samples are taken from a patient presented with heterogeneous tissue distribution. Sencondly, the section plane bias : the pathological section obtains diagnostic information only from a “specific” section plane. Touch print smear (TPS) of the retrieved sample can provide a backup message of the quality and quantity of spermatogenesis especially in non-obstructive azoospermia (NOA) patients. Thirdly, the resolution bias: sometimes, it is not easy to differentiate mature sperm from spermatid in HE stain pathological slide. So NOA patients with late maturation arrest (LMA) might occasionally be diagnosed as normal spermatogenesis. However, a backup TPS finding of the retrieved tissue, the appearance of mature sperm up on the TPS will give sufficient evidence for normal spermatogenesis. Fourthly, the diagnostic criteria bias. The pathologists might use a criteria different from the urologists. In conclusion, the diagnosis of NOA should be based on careful interpretation of the pathological slide and facilitated with all possible related methodologies. TPS is helpful to serve this function. Repeat testis biopsy or application of mTESE are essential for confirmation of sperm presence in patients with NOA and prepared for further ICSI treatment on their female partners.

Management of sleep disorder in elderly patients with urological disease

老年泌尿科病患的睡眠障礙處置

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Sleep is the body's rest cycle of 7-8 hours in healthy adult characterizing as a very complex physiological and behavioral process under a state marked by bouts of lessened consciousness, lessened movement of the skeletal muscles and slowed-down metabolism. Sleep disorder has very important effects on fatigue resolve, growth, endocrine, immune, cardiopulmonary, metabolic function, general health and eventually life-span. Prevalence of insomnia in elderly revealed as persistent insomnia in 10-15% and sleep disorder in 40-70%, which is basically accompanied with decreasing melatonin secretion as a person ages

Urological diseases related with sleep disorder are nocturia, overactive bladder, benign prostate hyperplasia, bladder & prostate cancer, cystitis, prostatitis, neurogenic bladder, urethral stricture, nocturnal polyuria, late onset hypogonadism, et cetera. Of these disorders, nocturia is one of the most bothersome self-reported insomnia in the elderly which is associated with poor quality of life.

Voiding and sleep patterns should be strictly evaluated in elderly patients to define which of urological disease or sleep disorder is primitive factor. Various medical options to control voiding and/or storage symptoms with sleep disorder have chosen as monotherapy or combination therapy including alpha-blockers, anticholinergics and antidiuretic hormone for urinary symptoms as well as good sleep hygiene practice of sleep disorder and hypnotics for insomnia. Therefore, to clarify underlying disease to cause patient's chief complaint is essential resulting to maximize therapeutic results.

This lecture will provide pathogenesis, diagnostic approach, ideal pharmacologic treatment with underlying action mechanism and cognitive behavior therapy in elderly with simultaneous sleep disorder and urological disease.

Roles of testosterone replacement therapy in men's health

睪酮補充在男性健康的角色

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Background

Androgens play many biological actions in the central and peripheral organ systems. Testosterone replacement therapy (TRT) may have significant benefits on pathological conditions that associated with testosterone deficiency (TD). On the other hands, diagnosis and treatment of late onset hypogonadism (LOH) syndrome are still having many controversies in real world. In this talk, I would like to summarize effects, safety and clinical roles of TRT on men's health through all men's life stages. I will also present challenges for management of LOH syndrome.

Results:

1) Effects and safety of TRT. Based on recommendations by corresponding international societies, TRT could profit with regard to obesity, metabolic syndrome, type 2 diabetes mellitus, sexual function and osteoporosis. Potential adverse effects of TRT on cardiovascular disease, prostate cancer. These effects and safeties remain to be investigated in large-scale prospective studies.

2) **Management of** LOH symptoms in real world. However, backgrounds of self-referred patients in our clinic are different from those that were discussed in the recommendations. Chief complains of our patients are depressive symptoms and loss of energy in relative-younger patients and physiological symptoms such as hot flash and sweating in elderly patients, respectively. In addition, we experienced undiagnosed depression, other endocrinal and neural diseases. We have to manage these significant clinical problems for men's health, although some symptoms are not associated with TD directly.

Recent our challenge is to apply TRT and daily PDE5-I for loss of energy and vigor (LOVE) syndrome. TRT and daily PDE5-I alleviated symptoms of LOVE syndrome. Recovery of morning erection by treatment made favorable effects on energy, self-confidence.

Conclusion

Management of self-referred patients for LOH should include individual evaluation of co-morbidities and careful risk versus benefit assessment. TRT has significant role in management of these patients, although some symptoms are still requiring effective treatment.

Erectile function after robot-assisted radical cystectomy

機器人輔助膀胱根除手術後之勃起功能

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Sexual dysfunction after radical cystectomy (RC) is a frequent, though commonly overlooked symptom for both men and women. The RC is associated with significant morbidity and a high prevalence of postoperative erectile dysfunction, which may have a major effect on quality of life, especially in younger patients. Improved oncological outcomes and the rising number of bladder cancer survivors mandate physicians to closely address and evaluate post-surgical sexual dysfunction and offer goal-directed treatment.

However, no studies have yet specifically evaluated continence and erectile function outcomes of RARC. Since all of the previous studies are retrospective data, the possibility of selection and recall biases is inevitable. According to the experience of korea university, 18 patients (37.5%) had preoperative IIEF5 score of 12 or more among 48 patients. Of these, 15 patients (83.3%) underwent NBV sparing, and 11 patients (73.3%) maintained potency at 1 year postoperatively, and 6 patients (54.5%) who did not receive PDE5 inhibitor.

Meanwhile, nerve-sparing cystectomy does not just increase the chance of maintaining erectile function. In men who had an attempted nerve-sparing operation, continence rate was better than in those who did not in a few studies. This results from preservation of the afferent intrapelvic anatomic sensory nerve supply to the pelvic floor and external urethral sphincter with preserved urethral sensation.

Extensive knowledge about pelvic anatomy and nerve-sparing surgical techniques in men is well understood from studies about prostate anatomy and nerve-sparing prostatectomy. Therefore, robotic cystectomy is expected to have advantages in terms of erectile function as well as continence considering robotic prostatectomy.

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肥胖治療新進展

Advancement in Obesity Treatment

時　間：107年6月30日　　　13:30~17:30
Time：June 30, 2018　　　13:30~17:30

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

肥胖治療新進展
Advancement in Obesity Treatment

Pathogenesis of NAFLD and obesity

非酒精性肝臟疾病與肥胖之致病機轉

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The global rise in the prevalence of obesity and associated co-morbidities such as non-alcoholic fatty liver disease (NAFLD) represents a major public health concern. The biological response to increased consumption of palatable foods or a reduction in energy expenditure is highly variable between individuals. A more detailed mechanistic understanding of the pathways involved in the development of obesity and NAFLD in susceptible individuals is critical for identifying effective mechanism-based preventative and therapeutic interventions.

Specifically, NAFLD is characterized by excessive fat accumulation in the liver. It ranges from simple steatosis to its more aggressive form, non-alcoholic steatohepatitis (NASH), which may develop into hepatic fibrosis, cirrhosis, or hepatocellular carcinoma. The increasing incidence of NAFLD is tied to the obesity epidemic and the subsequent metabolic derangements brought along with it. The pathogenesis of NAFLD/NASH is considered to be multifactorial and complex and is influenced by lifestyle habits, nutritional factors, and genetics. In particular, the Patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene has been recently recognized as the most important functional gene polymorphism in the progression of NASH. Moreover, epigenetic alterations are involved in the regulation of hepatic lipid metabolism, insulin resistance, mitochondrial damage, oxidative stress response, and the release of inflammatory cytokines, all of which have been implicated in the development and progression of NAFLD. Accordingly, integrated response among multiple organs with multiple pathways involvement but not "two-hit" theory might account for the genuine pathogenesis for NAFLD/NASH.

Management of NAFLD/NASH patients

非酒精性脂肪肝臟疾病之治療

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Non-alcoholic liver disease (NAFLD) has recently been recognized as the most prevalent liver disease worldwide. It is also on a trajectory to become the most common indication for liver transplantation. Non-alcoholic steatohepatitis (NASH) was defined by histopathologic evidence as an extreme form of NAFLD. NASH has been a histologically defined disease, characterized by hepatic steatosis and inflammation with variable presence and severity of Mallory's hyaline, balloon degeneration, and, most important clinically, fibrosis. NASH patients had higher overall mortality compared with controls, and most deaths were due to cardiovascular events. In addition, Asian people are more prone to metabolic syndrome (MetS), DM and NAFLD than other races. The achievements of NASH studies have been vigorously and successfully explored, from basic research to translational application. The efforts will much elucidate the real scenario of the important liver disease.

NASH has become the new emerging liver disease in Asia-Pacific as well as Westerns. Vigorous studies in terms of epidemiology, pathophysiology, and managements have been performed in the past years. A number of large clinical trials designed to identify effective and safe treatments for NASH and liver fibrosis are in progress. The efforts will much reinforce the current knowledge of the disease.

Medical nutrition therapy for weight control

體重控制之臨床營養療法

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Medical nutrition therapy (MNT) is a key component of diabetes management. The importance of balancing macronutrients, reducing carbohydrate load, lowering glycemic index, and implementing an overall healthy dietary pattern are emerging as better approaches for MNT in diabetes. Recent research points to improved glycemic control, reduction in body weight, and improvement in many cardiovascular risk factors when these approaches are provided in a structured nutrition plan by registered dietitians or health care providers. Structured nutrition plan includes specified menus, snack list and diabetes-specific formula within a hypocaloric diet. For optimal results structured nutrition plan should be coupled with cognitive behavioral modification and structured exercise plan that include stretching, aerobic and resistance training. This presentation discusses the current evidence about the role of sensible nutrition in diabetes and obesity management. Specific eating plans for weight reduction and for patients with type 1 diabetes will be also discussed.

Endoscopic management of obesity

肥胖之內視鏡治療

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Obesity and metabolic disease have reached pandemic proportions; yet to date non-surgical treatment modalities focusing on life-style interventions or pharmacotherapies have failed to achieve sufficient weight loss or have weight independent impact on the metabolic consequences of obesity as they have not addressed the pathophysiologic underpinnings of metabolic disease nor adequately targeted the multiple redundant pathways that controls energy intake and expenditure. Flexible gastrointestinal endoscopy offers an ever-expanding menu of minimally invasive alternatives to surgical interventions, through procedures developed to address obesity and metabolic disease. Gastroenterologists are well positioned to manage obesity given their broad-based medical knowledge, understanding of gastrointestinal physiology, and training in endoscopic techniques. Multiple efficacious medical devices, such as intragastric balloons, endoscopic suturing/plication devices, aspiration therapy, bypass liners, and mucosal resurfacing technologies are at various stages of development and some in clinical practice. When offered as part of multidisciplinary comprehensive program, endoscopic bariatric and metabolic therapies hold the promise of providing the next major breakthrough in gastrointestinal endoscopy and obesity.

Surgical management of obesity

肥胖之手術治療

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Morbid obesity and its related comorbidities has become one of the challenging threats to the public health worldwide. In comparison with behavior or medication therapy, bariatric surgery is currently the only evidence-based treatment for morbid obesity.

Two common performed weight loss procedures include laparoscopic Roux-en-Y gastric bypass (LRYGB) and sleeve gastrectomy. In Japan, due to the concern of high incidence of gastric cancer, Roux-en-Y gastric bypass is not recommended and not covered by the insurance. Another surgical procedure, laparoscopic sleeve gastrectomy with duodenojejunostomy (LSG-DJB) as an alternative to LRYGB, has become more popular in the treatment of type 2 diabetes in Japan.

The topics of today's speech include current evidence and consensus of surgical treatment of morbid obesity, hormonal mechanisms of diabetes resolution after bariatric/metabolic surgery, surgical treatment of type 2 diabetes in obese and non-obese patients, and management of complications after bariatric surgery.

Microbiota and metabolic change after GI tract surgery

胃腸手術後之代謝症候群與腸道微生物變化

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The gastrointestinal (GI) tract and gut microbiota play an important role in nutritional homeostasis and metabolic control. Human microbiota associated with metabolic syndrome and obesity show an increase in the *Firmicutes/Bacteroidetes ratio*.

Bariatric surgery which modified upper GI tract structure and function has widely demonstrated a bene¬ficial effect on obesity and type II diabetes and is associated with the increased bacterial species richness and diversity, esp. in post RYGB subjects (*increased Proteobacteria, Bacteroidetes, Akkermansia muciniphila, decreased Firmicutes*).

Propensity score-adjusted analysis showed that gastric cancer patients who received subtotal gastrectomy with B-II was associated with increased DM remission when compared with those with B-I. Gastric cancer patients with DM and a BMI between 30 to 35 showed higher DM remission rate esp. in RYGJ patients, followed by B-II, BI anastomosis. Our study showed that early gastric cancer patients after subtotal gastrectomy with RYGJ had a lower occurrence of metabolic syndrome and type II DM than the controls during long term (> 5 years) follow-up. In parallel with the metabolic improvements, gut microbial richness and diversity also significantly increased after subtotal gastrectomy with RYGJ.

Studies showed that patients with loss of the colon after surgical resection exhibit some characteristics of the insulin resistance. However, colectomies or colostomies are not significantly associated with BW loss in obesity or DM patients. Our study showed that early colorectal cancer (CRC) patients after curative partial colectomy with right hemicolectomy (RH), but not low anterior resection (LAR), had a higher occurrence of metabolic syndrome than the controls during long-term follow-up. In parallel with the metabolic syndrome, gut microbial diversity also significantly decreased after RH. However, the diversity of gut microbiota significantly increased after LAR than the controls.

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醫學人工智慧化：現在與未來

Medical AI: Current and Future

時 間：107年6月30日　13:30~17:30

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醫學人工智慧化：現在與未來
Medical AI: Current and Future

Computer artificial intelligence application direction and challenge on medical area

電腦人工智慧於醫療應用之現況與方向

Michael J Chang
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Microsoft Artificial Intelligence Research and Development Center, Taipei, Taiwan, ROC
微軟 台灣人工智慧研發中心

Computer Artificial Intelligence has been widely adopted in many areas worldwide. With the recent technology evolvement and advancement in Cloud, mobile devices, Big Data, algorithms, and use of hardware computing power, Computer Artificial Intelligence is growing beyond the traditional Computer Artificial Intelligence. With the rapid growth of Computer Artificial Intelligence technologies in the past few years, many challenges, such as laws and ethics, also surface and waiting to be solved.

It is widely confused that Computer Artificial Intelligence will replace the role of human being. The human ingenuity is the core of the technology advancement. The Computer Artificial Intelligence applications will not find its real impact without the human ingenuity.

There are many Computer Artificial Intelligence applications with proven initial results in Smart Manufacture, Smart City, and Medical areas. Using Smart Manufacture as example, it is proven that Video Imaging Computer Artificial Intelligence can significantly improve manufacturing defect detection efficiency and effectiveness. On the Medical front, many research institutes and business have started experiments using Computer Artificial Intelligence to help on many time consuming tasks. Many Computer Artificial Intelligence technologies have been widely applied on medical researches. The outlook of the medical Artificial Intelligence is promising.

Computer engineers and researchers may be fluent in Computer Artificial Intelligence technologies, but know very little in other domain areas. Many domain experts have deep industry knowledge and could not find the right area to experiment with the new technologies. It is clear that Computer Artificial Intelligence needs deep cross roles and cross functions collaboration to reach the best outcome.

The concerns of patients' privacy and lawful usage of medical data have become main blockers in medical Computer Artificial Intelligence researches. The current defined personnel that can lawfully access the medical data for research has hindered the progress of medical AI in Taiwan. It forces some researchers to obtain much needed medical data from external. The security of the data storage and research platforms are also areas for improvement.

AI in health care

人工智慧於健康照護之應用

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Artificial Intelligence (AI) has had a great impact on the healthcare field and will continue to transform health systems radically. Every healthcare professional should arm themselves with the knowledge to face these changes. In light of the newly developed AlphaGo program that win over one of the best Go chess players in the world, Artificial Intelligence (AI) is now back to the spotlight again. Given advice and warnings from some of the top minds like Elon Mush and Steven Hawkings, it seems inevitable that AI is going into a fast-pace development in the next few years and likely to impact every aspect of our lives very soon. This talk will describe the progress of AI applications in medicine in the past 30 years and discuss some possibilities about how Big Data and AI can go hand-in-hand in the future of health care for all the stakeholders, in terms of high-performance healthcare and precision medicine.

Medical AI: Academic perspective

醫學人工智慧：學術觀點

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National Chiao Tung University, Hsinchu, Taiwan, ROC
國立交通大學

With the thriving of deep learning techniques and high-speed graphics processing units, recent years have witnessed the beginning of a golden era of AI-based medical image analysis and diagnosis. Practicing smart healthcare and using artificial intelligence techniques to classify, segment, and track 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 AI-based diagnostic techniques for medical images. This talk takes practical clinical issues concerning atrial fibrillation, vertebral compression fracture, glaucoma, and intracranial metastasis as examples to explain how important deep/machine learning techniques may be integrated with clinical medical data and professional clinicians' accumulated experience. In the long run, the development of AI-based medical image analysis and diagnosis methods is expected to enhance the establishment of more instant, accurate, and comprehensive clinical diagnoses.

近年來，醫學影像之分析判讀，隨著人工智慧深度學習（Deep Learning）技術與高速圖形運算工具的迅速發展，已儼然邁入百家爭鳴的新紀元。實踐智慧醫療，透過人工智慧技術分類、圈註及追蹤病灶，從而減輕醫生繁重之影像判讀負擔並提升醫療品質，乃蔚為國際趨勢。例如深度學習範疇中之轉移學習（transfer learning）、YOLO、U-Net 等技術，刻正於醫學影像人工智慧領域迅速崛起，可與傳統機器學習技術相輔相成，應用於各類不同資料量等級的醫學影像，擴大醫學影像人工智慧判讀技術的光譜。本次演講以心房顫動、脊椎壓迫性骨折、青光眼、顱內轉移腫瘤等臨床議題為例，闡述如何將深度學習及機器學習領域中之重要技術與臨床醫學資料及臨床醫師多年累積之專業經驗結合，發展醫學影像之人工智慧判讀分析方法，期能協助臨床醫師做出更加即時、準確且全面之診斷。

On smart medicine revolution of the future

未來醫療的智慧革命

Ted Chang
張嘉淵
Quanta Computer Inc., Taoyuan, Taiwan, ROC
廣達電腦股份有限公司

In this speech, we, Quanta Computer as the world's biggest computer maker, shall share our vision regarding the smart medicine of the future from ICT industry aspects. The rapid development of High Performance Cloud Computing, Machine Learning and Big Data generated from "IoMT" (Internet of Medical Things) are making smart medicine in the science fictions possible in our life time now. No matter AI shall replace doctors or not, it shall surely create a whole new revolution in the future medicine.

Medial AI : ELS perspective

從倫理法律與社會的角度看醫學人工智慧化

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The introduction of AI to medical diagnosis and decision-making has the potential to greatly reduce the number of medical errors and misdiagnoses. However, as large dataset and machine learning techniques enable many predictions based on complex connections between patient characteristics and potential treatment results without identifying or understanding those connections, potential malpractice challenges will become more difficult and complicated than ever for physicians who rely upon AI and Big Data technologies. In other words, who should be responsible when a physician provides erroneous care at the suggestion of an AI system? This version of personalized medicine will not only usher in an unprecedented era of black-box medicine, it will also raise significant challenges with respect to privacy and data protection regulation. Similarly, we need to consider the ethical challenges inherent in implementing machine learning in medicine and healthcare if its benefits are to be realized. This presentation will tackle with questions as to how the introduction of AI systems will give rise to ethical, legal and social controversies, as well as what we shall do before the applications of AI systems in medicine and healthcare can be fully accepted into society.

AI is the new electricity: Why a platform approach to AI is the right approach for healthcare

美國的醫學人工智慧化

Pelu Tran
陳沛儒
Ferrum, San Francisco, CA, USA
Augmedix Inc., San Francisco, CA, USA

There are dozens of AI companies in healthcare founded every month, so figuring out which companies to work with can be overwhelming for even the most tech-savvy healthcare administrators and doctors. In this talk, Pelu will describe the different areas that AI is penetrating healthcare globally, where various approaches are finding success, and provide a framework for how doctors and hospital leaders can effectively create a successful AI strategy.

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腎臟精準醫學

Precision Medicine 3Bs in Nephrology: Bench to Bedside to Big Data

時 間：107年6月30日 13:30~17:30
Time：June 30, 2018 13:30~17:30

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

腎臟精準醫學
Precision Medicine 3Bs in Nephrology: Bench to Bedside to Big Data

Exploring the podocyte cytoskeleton: Start with basic research

從基礎研究探索足細胞骨架

Hsiao-Hui Lee
李曉暉
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國立陽明大學 生命科學系 暨 基因體科學研究所

Podocytes are highly specialized cells of the kidney glomerulus that wrap around capillaries and function as a key component of glomerular filtration barrier (GFB). They elaborate interdigitated foot processes (FPs) and form interconnections between FPs known as slit diaphragm (SD) for plasma ultrafiltration. Therefore, podocytes are exposed to permanent transcapillary filtration pressure and must therefore adhere tightly to the underlying glomerular basement membrane (GBM). The FP effacement, a hallmark feature of disease leading to nephrotic syndrome, involves disruption of the actin cytoskeleton leading to compromise of the SD and subsequent proteinuria. Loss of podocytes from the GBM underlies progression of chronic kidney disease (CKD).

Podocytes adhere to GBM via integrin-mediated focal adhesions (FAs) that connect with actin cytoskeleton. The Rho-GTPases are key players in the regulation of actin cytoskeleton and FA dynamics. Genetic studies reveal the cytoskeleton-associated mutations are related to the glomerular diseases. One of the first discovered cytoskeletal linked proteins causing focal segmental glomerulosclerosis (FSGS) was actinin-4 (ACTN4). Our laboratory had demonstrated that actinin-4 facilities Shp2 recruitment at FAs that promotes RhoA/ROCKII activation to enhance the intracellular tension in fibroblasts. By using a mouse temperature-inducible podocyte cell line, we further found that differentiated podocytes exhibited significant higher Shp2 and ROCKII activation accompany with the formation of strong FAs and actin stress fibers. Knockout of ACTN4 by CRISPR/Cas9 reduced Shp2 activation. Inhibition of Shp2 reduced ROCKII activation, FAs, stress fibers, and BSA-filtration ability of podocytes. Taken together, our results suggest the essential role of actinin-4 in Shp2/ROCKII activation that is crucial for cell adhesion and filtration function in podocytes.

Podocytes exhibit a unique cytoskeletal architecture that is fundamentally linked to their function in maintaining the kidney filtration barrier. The basic research according to the clinical and genetic finding shall lead to a better understanding of disease mechanisms..

Gut microbiome and dietary management in CKD patients

慢性腎臟病病人的腸道菌相與飲食治療

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Emerging evidence suggests that intestinal dysbiosis plays an important role in host inflammation locally and systemically. Such pathological condition is even more prevailing in patients with chronic kidney disease (CKD). Of note, indoxyl sulfate (IS), a gut-derived uremic toxin, is notorious for its pro-inflammatory feature in CKD patients. IS accumulates in the body as the urinary excretion of uremic toxins is impaired, and further worsens the kidney function in a vicious cycle to CKD.

Dietary restriction in vegetables, fruits, and yogurt leads to the predominance of indole-producing intestinal microbial flora and further exaggerates the accumulation of IS in CKD patients. Recently, interventional studies have shown that the circulating level of IS can be reduced by dietary prebiotic and/or probiotic supplements. However, further randomized controlled trials are warranted to examine whether such beneficial effect of dietary prebiotic/probiotic supplements could be extrapolated to better hard outcomes in CKD population.

In CKD patient care, clinicians often focus on medication prescription but sometimes overlook the importance of dietary management on blood pressure, blood sugar, blood lipid, or even blood uremic toxins. This notion reflects one of most famous quotes of Hippocrates, father of modern medicine, “Let food be thy medicine, and medicine be thy food”. In this talk, I review and reappraise the value of dietary management as well as its link to gut microbiome and uremic toxin production in CKD patients. Furthermore, I would also like to emphasize the importance of achieving sufficient intake of dietary fiber by proper vegetable pretreatment and accurate fruit selection in CKD patients, instead of directly avoiding these potassium-rich yet fiber-rich and base-producing foods.

Precision medicine in nephrology: From bench to bedside

腎病精準醫學：從實驗室研究到臨床應用

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By taking individual variability into account, precision medicine aims to incorporate molecular signature with traditional clinical data to provided tailor treatment strategies to achieve each individual patient's best outcome.

Notably, biomarkers are the critical elements of precision medicine. With advanced multi-omics techniques, clinical informatics and bioinformatics, and systems biology, numerous biomarkers are proposed in the nephrology field. These biomarkers could be classified as:

1. Risk/susceptibility biomarkers
2. Noninvasive diagnostic biomarkers
3. Invasive diagnostic biomarkers for disease reclassification
4. Prognostic biomarkers
5. Predictive biomarkers for selection of treatment modalities
6. Monitoring biomarkers gauge treatment efficacy
7. Pharmacodynamic/response biomarkers and safety biomarkers

Herein, we will review the progress of innovative technologies and their application in precision medicine of nephrology encompassing:

1. Inherited renal disease
1. Glomerular disease
2. New chronic kidney disease classification
3. Renal transplantation

By integrating the multi-scalar data sets, the practice of nephrology would enter the new era of P4 medicine which stands for a Predictive, Preventive, Personalized and Participatory medicine (Lee Hood, Nature Biotechnology 2011).

The new era of artificial intelligence in dialysis patients

人工智慧的時代在透析治療的應用

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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. Dialysis is the process to remove daily producing waste products, (e.g., uremic toxins) from our body by diffusion from one fluid compartment to another through a semi-permeable membrane as well as water removal. However, 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.

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. Artificial intelligence using neural networks (NNs) has been used to solve complex problems without needing a mathematical model or an understanding of the mechanisms involved. The artificial neural networks belong to mathematical models resembling the human brain behavior. They are able to “learn” from the “stimulation or input” and produce adequate responses as a consequence of this learning process. They are already widely used in internet network or autopilot technique. Therefore, a well-established NN model to study and predict the change of hemodialysis parameters, laboratory data and even the patient outcomes. Try to understand the basic concepts of artificial neural models and know how to perform a complete application in hemodialized patients will be introduced in this presentation.

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醫學教育暨臨床實踐之最佳實證

Best Evidence Medical Education (BEME) & Clinical Practice

主辦單位：中華醫學會、臺北榮民總醫院
協辦單位：考科藍臺灣研究中心、國立陽明大學

時 間：107年6月30日 13:00~17:30
Time：June 30, 2018 13:00~17:30

地 點：台北國際會議中心 102 會議室
Place：Conference Room 102
Taipei International Convention Center

醫學教育暨臨床實踐之最佳實證

Best Evidence Medical Education (BEME) & Clinical Practice

How medical students learn on the wards: An exploration using micro-learning networks analysis

醫學生如何在病房學習：一個使用微觀學習網絡分析之探索

Mark Newman
紐曼 馬克
EPPI-Centre Social Science Research Unit, UCL Institute of Education, London, UK
英國倫敦大學學院教育研究院 政策實務資訊實證中心 社會科學研究部門

The lecture will discuss the methodology and finding of an ethnographic research project carried in a UK University Medical School and teaching hospital that explored how medical students learned ‘clinical skills’ during their clinical placements.

The research led to the development of a novel analytical approach ‘micro-learning networks’ based on Actor Network Theory. The theoretical basis of micro-learning network and key concepts with be explored and its application illustrated through the findings of the study.The lecture will discuss the implications key findings of the study that:

- Students spent large amounts of time trying unsuccessfully to create learning opportunities for themselves.
- The important role played by material actors in blocking student access to learning opportunities.
- The important role played by non-medical staff and junior doctors in facilitating micro-learning networks for students .
- The relative lack of influence of the medical schools planned curriculum and students learning activities whilst on clinical placement.

CAN-Implement. Pro–methodology and method for adapting guidelines for evidence-based practice

CAN 實例：專業方法學與方法調整臨床指引以應用於實證照護

Craig Lockwood
洛克伍德 克雷格
Implementation Working Group G-I-N, The University of Adelaide, Australia
澳洲阿德萊德大學 實證實踐團隊

This presentation will introduce CAN-Implement. Pro, starting with how it works and how to get the best use out of software for guideline adaptation. In addition, the presentation will introduce attendees to the Knowledge to Action Model, the role of implementation planning, how facilitation effectively used enhances the work of guideline groups, and how to take a strategic approach to selecting programs of guideline development or adaptation.

Challenges in evidence-based health policy

實證健康政策之挑戰

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森 臨太郎
National Center for Child Health and Development, Cochrane Japan, Japan
考科藍日本國家兒童健康與發展中心

Evidence-based approached have been implemented and penetrated well in healthcare and it has significant impact on health policy and system, particularly on assessment and development of these.

The lecture covers the basic concept and brief history of the development and discuss the way forward.

From evidence-based medicine to evidence-based public health and evidence-based policy

從實證醫學到實證公共衛生及實證政策

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衛生福利部 國民健康署

Evidence-based public health is defined as the development, implementation, and evaluation of effective programs and policies in public health through application of principles of scientific reasoning, including systematic uses of data and information systems, and appropriate use of behavioral science theory and program planning models. Evidence-based approaches within this context require an understanding of the complexities of organizational structures, interactions, and dynamics that influence decision making at the local, state, regional, and national levels within which public health operates and within which policies and programs are established. Using an EBPH approach can be beneficial because it provides assurance that decision making is based on scientific evidence and effective practices, helps ensure the retrieval of up-to-date and reliable information about what works and doesn't work for a particular public health question and provides assurance that one's time is being used most efficiently and productively in reviewing the best information available on the particular public health question. The method using in EBPH is not limited to quantitative studies but also qualitative studies and community/policy level intervention.

Quality improvement through knowledge translation

透過知識轉譯改善品質

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臺北醫學大學 考科藍臺灣研究中心

Quality improvement (QI) consists of systematic and continuous actions that lead to improvement in healthcare delivery systems and health status of targeted populations. There are several ways to approach the QI Process, such as PDSA (Plan, Do, Study, Act) cycle. Knowledge translation (KT) is a new approach making better clinical practice, it can also enhance quality of healthcare. Canadian Institutes of Health Research [CIHR], 2000 defined KT as "A dynamic and iterative process that includes synthesis, dissemination, exchange and ethically-sound application of knowledge to improve the health, provide more effective health services and products as well as strengthen the health care system. KT process can divided into two parts: knowledge creation and application cycle. The QI can be only achieved when completing two phases of KT together. First, synthesis the evidence through systematic review/ meta-analysis to point out the best existing clinical evidence and recommendations. Second, overcome the barriers in clinical setting, including insufficient healthcare workforce, healthcare providers' abilities to understand and apply evidence, limited resources, immature or misunderstood shared-decision making process…etc. Some strategies may enhance knowledge application, such as evidence-based implementation strategies, supportive leadership, tailored interventions, routinely quality indicators audit and feedback…etc. Effectiveness of knowledge translation can improve the quality of care. KT can also be a powerful tool in upgrading health policy and guide the correct direction to improve the population health.

This lecture contents: (1) KT and QI; (2) Definitions and characteristics of KT; (3) KT Models; (4) Barriers and effective strategies of KT; and (5) Health Policy; (6) Examples sharing and discussion.

Make evidence-based practice individualized and smartater

讓實證照護個人化及更聰明

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Many researchers have recognized the importance of assigning distinct weights to individual adverse events in a composite end point. However, an adequate weighting approach have not been developed for the application on trial data. Here we develop an approach by utilizing two metrics, the disability-adjusted life-years (DALYs) developed by WHO Global Burden of Disease Project (GBDP) and the lifetime cost of medical care reimbursed by Taiwan's National Health Insurance, separately as the weighting values. We provided an example of the approach by integrating five clinical outcomes, myocardial infarction, ischemic stroke, intracranial hemorrhage, gastrointestinal bleeding, and all-cause death, into the composite in previous clinical trials on novel oral anticoagulation; and to evaluate the overall effect on a composite end point by performing a meta-analysis. The aggregative data from randomized controlled trials comparing non-VKA oral anticoagulants (NOACs) with vitamin K antagonists (VKAs) in patients with nonvalvular atrial fibrillation was used in this practice. The age-standardized DALYs or lifetime medical cost was incorporated into individual end points by multiplying the number of events in each outcome by the relative DALY value or cost value, and then summing over all weighted events. Considering uncertainty in assignment of preference weights, pooled estimates were further summarized after conducting aggregative analyses on the more numerous integrated data based on 1000 resampling weights derived from an appropriate distribution. Our results demonstrate that differential weighting of clinical end points is indeed required, which would correctly reflect the impacts of a particular therapy on the integrated and clinically weighted composite end point for patients or health policy

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輻射醫療處置暨核醫診療研討會

Symposium of Radiation Emergency Management and Radionuclide Theranostics

時　間：107年6月30日　　13:30~17:30
Time：June 30, 2018　　13:30~17:30

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

輻射醫療處置暨核醫診療研討會

Symposium of Radiation Emergency Management and Radionuclide Theranostics

Implications of INER biodosimetry lab. In nuclear accident

核研所生物劑量實驗室在核意外之應用

Kang-Wei Chang
張剛瑋
Division of Isotope Application, Institute of Nuclear Energy Research (INER), Taoyuan Taiwan, ROC
核能研究所 同位素組

Personal Biological Laboratories should plan the staff to receive dose as a later dose assessment and management to ensure that the individual dose of radiation-related operations. There are about 44,000 radiation workers in Taiwan, including in nuclear power plants, industrial and hospital areas. In order to measure the accidental exposure of radiation, it is necessary build a biological dosimetry laboratory. When exposed with radiation accident, the biological analysis could as exposure dose assessment, and as a follow-up medical care.

International studies on the current bio-dose-related effects of individuals; biological dosimetry by chromosome analysis is a quick, simple and effective method. In INER (institute of nuclear energy research) had established chromosome variation analysis of the relevant discrimination method, from 2012 to 2018, we were completed five dose-effect curve, and combined into a standard curve for the standard curve. We also participated in the International Competency Test with Canadian Ministry of Health, as well as received ISO17025 Laboratory certification. Expect to become a credible and internationalized national laboratory in biological dosimetry.

Leading countermeasures against radiation disaster and nuclear medical application after Fukushima nuclear power plant accident

針對核能災害的對應措施與相關醫療處置：福島事件的啟示

Shunichi Yamashita
Nagasaki University, Nagasaki, Japan and Fukushima Medical University, Fukushima, Japan

Seven years have passed since the complex disaster of the Great East Japan earthquake and its aftermath, the Fukushima Daiichi Nuclear Power Plant accident. Various issues, including not only the importance of emergency radiation medicine but also the public response to residents especially to those who lived in the affected area, have been revealed in the initial chaos and confusion. Ways to engage with the problems of radioactive contamination, the so-called "existing exposure situation" (a situation in which both the exposed dose remains higher than public dose limit (1mSv/year) during normal conditions and extended periods of time are required to further reduce the radiation dose), have also manifested as changes in individual action were caused by a difference in recognition and understanding of these problems. While difficult conditions and long-term mental and emotional stresses for evacuees continue, it is gradually becoming possible to make level-headed decisions and act calmly.

First we need to follow the global consensus on radiological protection standards introduced by the UNSCEAR, ICRP, WHO and IAEA. To prepare for and respond to nuclear accident more effectively and efficiently, we further need to improve the comprehensive countermeasures against radiation disaster and nuclear medical application.

In Japan, a new governance and structure of nuclear disaster countermeasures was established by Nuclear Regulatory Agency from August 2015. Here, the overall scope and structure of radiation protection and safety will be overviewed on a basis of our own experience in Fukushima, Japan.

Role of nuclear scintigraphy in SIRT-NTUH experience

核醫影像在釔 90 體內放療的角色：台大經驗

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The purpose of radiation therapy is to reduce tumor burden while preserving normal tissues from injury. Our experiences (NTUH) in selective internal radiation therapy using Yittrium-90 resin microspheres will be discussed, especially focusing on the role of nuclear scintigraphy in treatment planning. Strategies to minimize radiation-reduced injury will be discussed.

Radiation concern and perspectives of Y-90 SIRT

釔 90 體內放療的相關輻射防護議題與未來展望

Ko-Han Lin

林可瀚

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臺北榮民總醫院 核子醫學部

Yttrium-90 microsphere selective internal radiation therapy (Y-90 SIRT) is an emerging treatment method for advanced hepatocellular carcinoma and metastatic hepatic malignancies. This therapy is rapidly expanding throughout the radiology and nuclear medicine communities since introducing to Taiwan. Since 2008, we performed more than 300 treatments using Y-90 SIRT in Taipei Veterans General Hospital and also provided technical instructions to other institutes.

Two kinds of Yttrium-90 microspheres are available for SIRT. One is manufactured by Sirtex with Y-90 isotopes labeled on the surface of resin spheres and the other is manufactured by BTG with Y-90 embedded in the glass matrix. Some principles of treatment are similar for these two microspheres, such as trans-catheter arterial delivery, estimation of lung shunt fraction with Tc-MAA simulation, and post-treatment scanning. However, other issues differ significantly between these two microspheres because of different characteristics, delivery devices, and dosimetric formula.

For the glass microspheres, the activity of dose vial is fixed and its delivery system is seal-designed, which brings on less radiation protection concern. However, the radioactivity administrated might be less flexible. On the contrary, the resin microspheres provide on-site adjustment more flexible, but with more concern of employee radiation exposure.

In this section, I will introduce the several concerns of two kinds of Y-90 microspheres and future perspectives of Y-90 SIRT for liver cancers in Taiwan.

Reintroduction of RAI therapy to RAI refractory thyroid cancer

放射碘治療在難治性甲狀腺癌的再導入

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Although most differentiated thyroid cancers show excellent prognosis, treating radioiodine refractory differentiated thyroid cancer is challenging. Various therapies, including chemotherapy, radiotherapy, and targeted therapy, have been applied for treating radioiodine refractory differentiated thyroid cancer but show limited effectiveness. The pathogenesis of thyroid cancer is closely associated with genetic mutations, rearrangements and epigenetic alterations, which activate certain signaling cascades, which might produce silencing of iodide metabolizing genes. Blockade of the signaling cascades may lead to redifferentiation of radioiodine refractory cancers that are respond to radioiodine therapy. Redifferentiation followed by radioiodine therapy might be a promising new alternative therapy for the radioiodine refractory differentiated thyroid cancer.

In this presentation, clinical values of redifferentiation on the radioiodine refractory differentiated thyroid cancer and discovery and development of the redifferentiation agents using molecular imaging techniques will be discussed.

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腹腔鏡直腸癌手術的進展

Update of Laparoscopic Surgery in Rectal Cancer

協辦單位：中華民國大腸直腸外科醫學會

時　間：107年6月30日　　13:30~17:40
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地　點：台北國際會議中心 201BC 會議室
Place：Conference Room 201BC
Taipei International Convention Center

腹腔鏡直腸癌手術的進展

Update of Laparoscopic Surgery in Rectal Cancer

Conventional laparoscopic versus transanal total mesorectal excision (taTME) for rectal cancer after neoadjuvant chemoradiation : Long term follow-up result

經肛門與傳統腹腔鏡直腸癌手術的長期預後分析

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Since its earliest reports, transanal total mesorectal excision (taTME) has attracted attention regarding its potential role in rectal surgery. Several study series have established that the direct and targeted approach of natural orifice transluminal endoscopic surgery (NOTES) is fully feasible in rectal surgery. On the other hand, it has also been established that laparoscopic rectal surgery is demanding in both tecnique and experience, as reflected by the higher conversion rates reported for laparoscopic rectal cancer surgery: 17 % in the Colorectal Cancer Laparoscopic or Open Resection (COLOR) II trial, and up to 29 % in other documented study series. Thus, whe- ther performed via an open or conventional laparoscopic approach, TME encounters many challenges, including narrow pelvic anatomy, male sex, bulky mesorectum, and high body mass index (BMI). This is where taTME may offer some elegant solutions.

Our group previously reported our preliminary experiences with taTME and reflected on its feasibility, rapidly evolving nature, and great potential for further development. In our published matched case–control study for post irradiated rectal cancer in 2016, demonstrated that taTME is safe and feasible. Compared with LapTME, taTME not only achieves identical circumferential margin status without compromising other operative and quality parameters but also benefits patients by achieving a longer distal margin. Thus, taTME has the potential to become an option in managing irradiated rectal cancer.

In the presentation, the long term follow-up data of conventional laparoscopic and taTME groups will be analyzed, and recent progression and published evidence will be reviewed to establish more solid fundamentation for this rapid evolving surgical technique.

Laparoscopic rectal surgery beyond TME to locally advanced rectal cancer

局部侵犯性直腸癌的腹腔鏡手術探討

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Background and Aim

Laparoscopic rectal surgery is spreading quickly, but some large randomized control trials in terms of long-term outcomes of this surgery have been reported both as favor and against. However, this surgery in our institution is now standard technique because merit of the magnified vision and technical developing. In such circumstances, even further locally advanced rectal cancer is treated by laparoscopy including resection of the adjacent structures or lateral lymph node dissection. We are showing our videos of laparoscopic extended TME procedure in lecture.

Procedure

Laparoscopic TME is an essential procedure to rectal cancer cases. If the tumor invades to pelvic nerve plexus or neurovascular bundles, those nerves are resected associated with mesorectal fascia. For the cases of invading to the prostate or the urinary bladder, total pelvic exenteration (TPE) under laparoscopy is tried. In female, uterus is casually resected via laparoscopy for the case of invasion. For the cases of lateral lymph node positive, lateral lymph node dissection of the illness side is performed. After taping of the ureter, lumbar muscle just caudal to the external iliac artery and vain is exposed. Uretal-hypogastric nerve plane is preserved in median side and obturator region (station number 283) and around the iliac artery (station number 263) are dissected.

Results

The mean operating time and estimated blood loss of 48 cases of TME with a part of adjacent organs (pelvic plexus, seminal vesicle, neuro-vascular bundles, etc,) were 447 min. and 180 g, respectively. Those of 59 cases of TME with invaded uterus were 327 mon. and 100 g, respectively. And those of 11 cases of TPE were 831 min. and 650 g, respectively. There were 2 open conversions in this series but not in the laparoscopic TPE. No positive dissection margin was encountered in pathology in this series. The mean operating time and estimated blood loss of 253 cases of lateral lymph node dissection were 462 min. and 110 g, respectively. The postoperative complications over grade III in Clavian-Dindo classification were 9 of the 48 cases (18%), 4 of the 59 cases (6.9%), 3 of the 11 cases (27%), and 29 of the 253 cases (17%), respectively. No mortality was encountered in our series.

Conclusion

Based on TME, resection of the adjacent pelvic organ and the lateral lymph node dissection via laparoscopy are likely to be carried out safe both in technically and oncologically.

Rectal cancer surgery: From open to transanal

直腸癌手術：從傳統開放式手術到經肛門直腸切除

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The combined of laparoscopic and technology has changed the practice of rectal surgery. In colon surgery, laparoscopic colectomy is current the golden standard of treating colorectal disorders. Application of minimally invasive surgery for the treatment of rectal cancer has been controversial, both randomized laparoscopic versus open trails for rectal cancer surgery from the United States and Australia did not make its non-inferiority, and also The ROLARR laparoscopic robotic rectal resection versus laparoscopic rectal resection trail did not showed its superiority of robot in conversion to open surgery. Minimally invasive approach for rectal cancer surgery is associated with steep learning curves; implementation has been a long process, this result in higher conversion rate in some series. Currently, transanal TME is an option to overcome some of the potential challenges of rectal mobilization and transection is to perform the mobilization from below. This talk will focus on the evolution of rectal cancer surgery, and introduction to varies technique on treatment of rectal cancer.

Laparoscopic lateral node dissection for advanced rectal cancer

腹腔鏡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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Simplification and standardization of a complicated technique are particularly important for laparoscopic total mesorectal excision (TME) and lateral pelvic node dissection (LLPND) of locally advanced rectal cancer. We developed the technique for LLPND from 2011 and assessed its feasibility.

Two areas of lateral pelvic region are dissected. One of which is the area along the obturator artery running in front of the internal obturator muscle. The other is the area along the internal iliac artery and its visceral branches which is enveloped in the endopelvic fascia with pelvic organs and its dominant nerves. It is considered that carcinoma at advanced rectal cancer has dual lymphatic drainage of the middle rectal artery (superficial branch) -neurovascular bundle -inferior vesical artery -internal iliac artery and middle rectal artery (deep branch) -inferior vesical artery -internal pudendal artery and in addition, lymph node mainly exists proximal side of inferior vesical artery.

From 2011, 136 patients with rectal cancer underwent TME with LLPND. These patients included 43 females and had a mean age of 63.0 years and body mass index of 22.8 kg/m2. Average operation time and blood loss were 403 minutes and 120 ml respectively. Average number of harvested lymph nodes of lateral pelvic region was 12.3. Lateral pelvic node metastases existed in 18 (13.2%) patients. Clavien-Dindo grade 2 dysuria was 15.4% and two of the patients required urinary intermittent catheterization.

TME with LLPND can be safely performed by simplification and standardization of our surgical procedure.

Rectal cancer treatment: Still in evolution

演進中的直腸癌治療

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Rectal cancer outcomes have significantly improved in the last 30 years. The implementation of total meso-rectal excision (TME) led to a drastic reduction in loco-regional recurrence (LR).

However, in some patients with middle or low rectal cancer, especially in those with severe obesity or a very narrow pelvis, TME procedure can encounter unexpected difficulties. In 2010, a down-to-up approach, transanal total mesorectal excision (taTME), was introduced with the aim to achieve better outcome. However, the results of taTME for rectal cancer, especially pathological outcomes, still remain controversial. Besides, the role of lateral lymph node in rectal cancer treatment is still elusive.

The quality of the surgical specimen and the long-term oncological outcomes of laparoscopic surgery are equivalent to those of open surgery. However, laparoscopic surgery for rectal cancer is technically demanding, limiting its application in nonspecialized centers. Robotic surgery for rectal cancer is an emerging technique. A robotic system facilitates precise dissection and maneuvering in a narrow space, such as the pelvis. The drawback of robotic surgery includes high cost and increased OR time, so the role of robot in rectal cancer surgery will be reviewed.

Neoadjuvant therapy also improved the treatment outcome of rectal cancer. However, the interval between CRT and surgery is still changing. The ideal adjuvant chemotherapy regimens are also in evolution for resected LARC. From experience of metastatic rectal cancer, the concept of total neoadjuvant therapy (TNT) is introduced. For rectal cancer, the treatment is still improving and more studies are warrant.

Human papillomavirus infections, anal precancerous lesions, and anal cancers in men who are living with HIV

愛滋病毒感染者的人類乳突病毒感染、肛門癌前病變，與肛門惡性腫瘤

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Anal cancers are rare in the general population. In the early era of highly active antiretroviral therapy (HAART), the risk of developing anal carcinoma *in situ* was 60 times greater in HIV-infected men than in the general population, and the risk of developing invasive anal cancer was 38 times greater. These higher rates did not abate during the years when HAART was used more widely. Oncogenic types of human papillomavirus (HPV), especially genotype 16, are found in more than 80% of anal carcinomas. Additionally, the association between oncogenic HPVs and histologically confirmed high-grade anal intraepithelial neoplasia has also been confirmed.

In Taiwan, the cumulative number of HIV infections exceeded 35,000 at the end of 2017. More than 85% of newly diagnosed HIV infections are men who have sex with men (MSM). Previous studies in Taiwan showed that 90% of HIV-infected men had anal HPV, 81% of whom had oncogenic anal HPVs. Among them, 23-30% had abnormal anal cytology, including atypical squamous cells of undetermined significance; low-grade squamous intraepithelial lesions; high-grade squamous intraepithelial lesions; and atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions. National Health Insurance and Research Database showed that men who had genital warts had 6 times to develop anogenital cancers, and, incident HIV infection was 284 per 100,000 py among patients who had condyloma acuminata. Until now there are no data to support HPV vaccination of men, including MSM, in Taiwan.

There is still a limited understanding of Taiwanese MSM who lived in a conservative society with traditional societal norms. This review aimed to address above issues and to assist the physicians in Taiwan to provide a comprehensive care for men who are living with HIV.

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老年憂鬱症診斷與治療研討會

Depressive Disorder in Late Life: Diagnosis and Treatment

時　間：107年6月30日　　13:30~17:00
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老年憂鬱症診斷與治療研討會

Depressive Disorder in Late Life: Diagnosis and Treatment

Depression in women: From menopause to aging

婦女與憂鬱症：從停經到老化

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Menopause transition and aging are associated with the occurrence of some physical and psychiatric symptoms. During this period, women become vulnerable to anxiety and depressive disorders.

The menopausal transition is marked by intense hormonal fluctuations, accompanied by vasomotor symptoms (e.g., hot flashes, night sweats), and psychiatric symptoms. Most prevalent psychiatric symptoms during this period were irritability, tearfulness, anxiety, depression, labile mood, lack of motivation, lack of energy, poor concentration and sleep disturbance.

The efficacy of estrogen therapy to alleviate vasomotor symptoms has been well documented. And antidepressants have well-established efficacy for treating menopausal mood symptoms including anxiety and depression. Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors can also be used as the second line treatment for hot flashes and diaphoresis.

Women are about twice as likely as men to develop depressive disorders. However, gender differences in geriatric depression have been studied inconsistently. In Taiwan, studies showed that old women are still more likely than men to become depressed. The etiology of geriatric depression involved intrinsic factors (such a genetic predisposing, age-related neurochemical changes, age-related neuroanatomical changes, vascular factors, reduction of cerebral flow, physical disease, pain,…etc.) and external factors (such as stress, loss and poor social support… etc).

Psychosocial Intervention is important in the treatment of geriatric depression. For example, reality orientation, remotivation, resocialization, sensory retraining, group activities, ….etc. Though medications are not so helpful in treating geriatric depression, all class of antidepressants have proven effective for geriatric depressive disorders. Antidepressants with less adverse effects and few drug drug interaction are preferred. For treatment resistant geriatric depression, augmentation with lithium, some new generation antipsychotics or even electroconvulsive therapy can be considered.

Management of treatment-resistant late-life depression

難治型老年憂鬱症的治療

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Depression is the most common psychiatric disorder in late life in Taiwan. The total prevalence rate of major depressive disorder and other depressive disorders was over 21% in the elderly in Taiwanese community study. Since depression not only increases risk of suicide, but also debilitates one's health and makes patient's functional decline, it causes severe care burden and poor quality of life in patient's family and often leads to considerable cost in the society.

Although pharmacological treatment can effectively alleviate or cure elderly depression, the rate of treatment-resistant among all late-life depressed patients is estimated from 12% to 20%. The treatment-resistant late-life depression (TRLLD) results in social burden and pushing up the total societal costs of depression. the unmet need for issues on the mechanisms of TRLLL and new therapeutic targets, existing and new treatment combination for TRLLD is worth discussing and researching.

The first issue of TRLLD prior to choice of drugs is definition of TRLLL or pseudo-resistant late-life depression including adherence or sufficient blood level of therapeutic drugs, comorbidity with physical diseases or mental disorders and chronic psycho-social stressor. The other important issue is how to find the relative factors of TRLLD such as comorbid with anxiety disorders or personality disorder, onset of age younger than 18 years, multiple of episode of depression, multiple times of admission and history of treatment resistance and how to put earlier prevention and special interventions of depression.

The evidence of effective treatment strategies for treatment resistant depression includes combination of antidepressant and atypical antipsychotics, adding thyroid or lithium on antidepressant treatment, ECT or r-TMS. Besides, the other evidences for management of TRLLD demonstrate that psychosocial interventions, e.g. problem-solving therapy, cognitive-behavior therapy, reminiscence therapy, or exercise can improve the effectiveness of TRLLD.

Detection of major depressive disorder based on EEG signals and machine learning

基於腦波及機器學習之憂鬱症快速偵測

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Major depressive disorder (MDD) is characterized by persistent sadness, hopelessness, and inability to feel pleasure in normally enjoyable activities (i.e., anhedonia). MDD is also associated with cognitive problems, including deficits in executive function and memory, and recent depression is a well-established risk factor for suicide. According to WHO, more than 300 million people suffer from depression, making it one of the leading contributors to the global burden of disease. To effectively treat MDD, a safe, objective, and convenient method for accurate diagnosis is essential. Electroencephalography (EEG) is increasingly recognized as a promising tool in this regard, because it is a well-established, inexpensive, and non-invasive method for assessing brain function. EEG has emerged as a tool for assisting with the detection of MDD.

In this talk, I will introduce a novel machine learning method based on EEG signals and a robust spectral-spatial EEG feature extractor called kernel eigen-filter-bank common spatial pattern (KEFB-CSP). The KEFB-CSP first filters the multi-channel raw EEG signals into a set of frequency subbands, then spatially transforms the EEG signals of each subband from the original sensor space to a new space where the new signals (i.e., CSPs) are optimal for the classification between MDD and healthy controls, and finally applies the kernel principal component analysis to transform the vector containing the CSPs from all frequency subbands to a lower-dimensional feature vector called KEFB-CSP. Our results show that KEFB-CSP outperforms other EEG features including the powers of EEG bands, and fractal dimension. The results also reveal that the 8 electrodes from the temporal areas gave higher accuracies than other scalp areas. The KEFB-CSP was able to achieve an average EEG classification accuracy of 81.23% in single-trial analysis when only the 8-electrode EEGs of the temporal area and a support vector machine (SVM) classifier were used. The voting-based results show that the mean classification accuracy of about 80% can be achieved by the KEFP-CSP feature and the SVM classifier with only several trials. These findings therefore suggest that this method has a great potential for developing an efficient (required only a few 6-second EEG signals from the 8 electrodes over the temporal) and effective (~80% accuracy) EEG-based brain-computer interface (BCI) system which may, in the future, help psychiatrists provide personalized and effective treatments for MDD patients.

Molecular imaging in geriatric depression

老年憂鬱症之分子影像學研究

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Molecular imaging is a non-invasive tool to investigate target molecules or biological processes in the living brain. It has been applied in neuroscience research and improving clinical management of neuropsychiatric disorders. In the presentation, I will review recent molecular imaging studies, mainly using positron emission tomography (PET) in geriatric depression. The imaging targets in these studies included regional cerebral blood flow, glucose metabolism, neuroreceptor binding, amyloid and tau proteins. The changes in these imaging markers and their potential roles in pathophysiology, relationship with clinical features and treatment effects were examined. Moreover, PET has been used to evaluate the interface between depression and dementia. The related challenges and possible future applications will also be discussed. In summary, molecular imaging not only help us further understand the pathophysiology of geriatric depression but also help to facilitate the development of better therapies.

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數位科技在耳科的運用

Digital Technology Usage in Clinical Otology

主辦單位：中華醫學會
協辦單位：台灣耳鼻喉科醫學會

時　間：107年6月30日　　13:00~16:40
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Place：3 Floor, Conference Room South Lounge
Taipei International Convention Center

數位科技在耳科的運用
Digital Technology Usage in Clinical Otology

Artificial Intelligence (AI) usage in clinical audiology

人工智慧 (AI) 應用於臨床聽力學

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The story of sci-fi movie “Minority Report” (Steven Spielberg's 2002) was based on the science fiction story (Philip K. Dick in 1956). The time of the story is set in 2054, but the situation can almost completely occur in 2018. The main key is Artificial intelligence (AI) that has made an amazing impact in the game, natural language, self-driving, education. As a scientific application, medicine naturally can not escape this trend.

IBM Watson was first "enrolled" in medical school at Columbia University in 2011, as well as at the University of Maryland School of Medicine. Watson has "read" dozens of textbooks, all of PubMed and Medline (two massive databases of medical journals) „ and thousands of patient records from Memorial Sloan Kettering. All together, Watson has analyzed 605,000 pieces of medical evidence, 2 million pages of text, 25,000 training cases and had the assist of 14,700 clinician hours fine-tuning its decision accuracy. If it's not already the world's best diagnostician, it will be soon. In the other way, the Smart Tissue Autonomous Robot (STAR) at John Hopkins University of Maryland successfully completed soft tissue surgery, which was performed around 45 million such surgeries every year in the United States. Compared to the STAR system, Da Vinci surgery appears to be human infancy, and surgeons will have strong competitors.

Through the establishment of a cloud-based service model and sharing experience of hearing aids application, we believe that the medical model for hearing loss rehabilitation with artificial intelligence components will soon appear, and it will be a breakthrough for the rapidly growing hearing-impaired population with aging.

Audio-visual signal processing for human-computer interface and its applications to facilitate better human-human communications

結合視覺聽覺之智能計算及其在增進口語溝通上的應用

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Background: Human communication is a process that occurs in both auditory and visual modalities. The role of visual information is particularly important when the auditory speech is processed in a less favorable signal-to-noise ratio. In the artificial intelligent area, the integration of audio and visual information has become a promising research direction. In the past, we have developed oral presentation training, emotion recognition, speaker recognition, and speech enhancement systems based on the integration of audio and visual information. The results show that using information from multiple modalities enables more effective human-computer interactions. More recently, we have applied the derived algorithms to facilitate human-human communications and obtained promising results.

Methods: We have established oral presentation training and speech enhancement systems based on the state-of-the-art deep learning models and multi-task learning algorithms. The oral presentation training system can be used as a training tool for hearing-impaired individuals to consistently and regularly practice in the speech-language intervention and aural rehabilitation process. The audio-visual system, which has shown to provide better speech enhancement capability over audio-only systems, can be suitably used in various types of assistive listening devices.

Results: For the oral presentation training system, we have been collaborating with the National Academy for Educational Research (NAER) to collect oral presentation video streams. Based on the collected data, we established the scoring system and tested performance. The results showed that the multimodal fusion of audio and video information improves the recognition over audio-only and video-only systems. For the audio-visual speech enhancement (AVSE) system, the results show that the AVSE model yields a notably superior performance compared with an audio-only speech enhancement model and two conventional SE approaches, confirming the effectiveness of integrating visual information into the SE process. In addition, the AVSE model also outperforms an existing audio-visual SE model, confirming its capability of effectively combining audio and visual information in SE.

Conclusion: In this presentation, we show two audio-visual multimodal systems: oral training and speech enhancement. These two systems have shown to considerably improve the human-computer interactions. Our current results show that these two systems are also helpful for improving human-human communications, especially for individuals with communication disability.

Improvement of speech intelligibility for cochlear implant recipients based on deep learning approach

以深度學習技術提升人工電子耳患者之語音理解力表現

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Cochlear implants (CIs) are surgically implanted electronic devices that provide a sense of sound in patients with profound to severe hearing loss. The considerable progress of CI technologies in the past three decades has enabled many CI users to enjoy a high level of speech understanding in quiet. For most CI users, however, understanding speech in noisy environments remains a challenge. In this talk, I will present the proposed approach, called NC+DDAE, to improve the performance of speech intelligibility in noisy listening conditions for CI recipients. In a series of comprehensive experiments, we conduct qualitative and quantitative analyses on the NC module and the overall NC+DDAE approach. Moreover, we evaluate the speech recognition performance of the NC+DDAE NR and classical single-microphone NR approaches for Mandarin-speaking CI recipients under different noise conditions. The experimental results of objective evaluation and listening test indicate that, under challenging listening conditions, the proposed NC+DDAE NR approach yields higher intelligibility scores than the two compared classical NR techniques, under both matched and mismatched training conditions. More specifically, when compared to the two well-known conventional NR techniques under challenging listening condition, the proposed NC+DDAE NR approach has superior noise suppression capabilities, and gives less distortion for the key speech envelope information, thus improving speech recognition more effectively for Mandarin CI recipients. The results of this study suggest that the proposed deep-learning based NR approach can potentially be integrated into existing CI signal processors to overcome the degradation of speech perception caused by noise.

Ear Scale App for hearing screening in the school-age children

聽力量值 APP 應用於國小學童聽檢

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Background: Unidentified hearing impairment is one of common problems in school-aged children. Early detection and diagnosis of these children is difficult and routine pure-tone hearing screening currently is the best choice.

Methods: A total of eighty-five school-age children in Tian-Mu Elementary School participated in this study. The Ear Scale App runs in IOS 10.3.3 devices employs ten stratified hearing scales form S1 to S10 for children, each hearing scale contains four test pure tones with adjacent scales differ from each other by 5dB HL ranging from 1dB HL(S1) to 46 dB (S10). The starting hearing scale of the App is S5 (1000, 2000, and 4000 Hz at 20 dB, and 500 Hz at 25 dB HL). The Ear Scale App determines 1000, 2000, and 4000 Hz at 20 dB, and 500 Hz at 25 dB HL for each ear. Ear Scale App introduction in youtube videos: https://youtu.be/5x6a_KmRjMc.

Results: PTA was calculated as the mean of hearing thresholds at 500, 1000, 2,000, and 4,000 Hz. For hearing screening, failure was defined as a PTA > 25 dB in either ear, so that a hearing scale of S1 – S5 was considered as pass and S6 – S10 as failure. Eighty-five school-age children were tested (170 ears). The Ear Scale App test was specificity of 100% in all four screening protocols. Sensitivity was 100% (PTA = 21 dB), 95.2% (PTA = 20 dB), 95.2% (PTA = 16.3 dB), 79.2% (PTA = 15 dB). False/Negative was 0% (PTA =21 dB), 4.8% (PTA =20 dB), 4.8% (PTA =16.3 dB), 4.8% (PTA =20.8 dB).

Conclusion: The Ear Scale App has ten stratified hearing scales (S1-S10) that a smartphone-based hearing test, is a quickly and easily operated screening tool for hearing loss in the school-age population. It can be recommended for initial hearing assessments and follow-up surveillance in school-age children.

Introduction of the digital auditory rehabilitation platform

數位化聽能復健平台介紹與應用

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Background: According to the national report, there are over 30% of the aged people who suffers from hearing impairment which mostly resulted from aging and noise exposure. Accordingly, our hearing impaired population is around one million. To improve these patients' communication ability, Proper amplification and deliberate rehabilitation are mandatory in our aging society.

There are 3 purposes in developing a digitalized auditory rehabilitation (AR) platform:

(1) Identification of hearing impairment/disability;

(2) Evaluation of amplification setting; and

(3) Facilitation of auditory rehabilitation.

Purpose: The aim of this study is to design a digital auditory rehabilitation platform for Mandarin-Chinese language. In order to facilitate the AR procedure, a digitalized evaluation system is to be developed. An internet-based protocol can also be promoted among our hearing health clinics for further investigation and data-sharing.

Methods: The procedures are listed as below consecutively: (1) Filing of Mandarin speech materials; (2) Establishment of clinical AR protocol; (3) Designing a digitalized AR platform; (4) Soft/hard-wares setting and calibration; and (5) Clinical testing of the AR platform.

Expectation: A digitalized AR platform based on Mandarin speech materials and protocol will be set up and applied to clinical auditory rehabilitation. As the clinical experience suggested, such a digitalized system could be applied in the hearing health clinics of the Mandarin-speaking population.

New era for otology: From NGS to gene therapy

精準醫學應用於臨床耳科學 (台北榮總)

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Hearing loss is one of the most common sensory disorders. It is estimated that more than 360 million affected people worldwide in 2017; among them, 32 million are children. The causes of hearing loss are divided into congenital causes and acquired causes. Congenital hearing loss can be found in 2-3 in 1000 births. Congenital hearing loss can be caused by genetic factors, and complications during pregnancy and delivery, including maternal infections (Cytomegalovirus, rubella, etc.), severe jaundice and asphyxia.

More than two-thirds of congenital hearing loss has an underlying genetic component. Genetic mutations over 100 genes can cause congenital nonsyndromic and syndromic hearing loss, and more than 400 syndromes have been identified to be correlated with hearing loss. Even though Sanger sequencing is still a good standard for DNA sequencing of suspected causative genes, Next-generation sequencing (NGS) technology offers the advantage of sequencing multiple genes in parallel with lower cost and higher time-efficiency and has quickly become a popular tool for targeted panel-based hearing loss diagnostics. NGS technologies are causing a shift in how otolaryngologist and medical researchers investigating hearing disorders, providing not only molecular diagnosis but also discovery of new disease-causing genes.

While sound amplification devices such as hearing aids can be helpful for most patients with hearing loss, cochlear implant is used some patients with profound hearing loss who cannot benefit from cochlear implants. Even though both hearing aids and cochlear implants have been seeing rapid improvements and advances in technology, there are still a lot of limitations for both devices in restoring the biological hearing process, and never be a cure.

With the understanding of underlying genetic deficits and the establishment of safer and more-targeted vector, personalized gene therapy has become a promising treatment for genetic deafness. We believe that with the advancement of diagnostic and therapeutic tools in precision medicine, hearing disorders caused by genetic defects will soon become treatable or curable in the near future.

「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

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Acute macular edema and peripapillary soft exudate after pancreas transplantation with accelerated progression of diabetic retinopathy

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ABSTRACT

Background. The effect of pancreas transplantation on diabetic retinopathy remains inconclusive. Herein, we report six patients with type 1 diabetes mellitus (DM) who underwent pancreas transplantation and developed acute macular edema and peripapillary soft exudate with rapid progression to proliferative diabetic retinopathy.

Methods. In this retrospective observational study, diabetic patients who underwent pancreas transplantation in a single medical center and developed symptomatic acute macular edema and peripapillary soft exudate within 3 months after the operation were enrolled. The complete ophthalmic course and medical records of the patients were retrospectively reviewed. Diabetic retinopathy and progression following treatment after pancreas transplantation were measured.

Results. Six Chinese women with type 1 DM were enrolled in this study. Mean hemoglobin (Hb) A1c was 13.4% prior to transplantation and decreased rapidly to 6.5% within 2 months postsurgery. The patients had no or mild pretransplant diabetic retinopathy and developed acute symptomatic macular edema and peripapillary soft exudate in both eyes after pancreas transplantation. All macular edema resolved either with or without treatment. Five cases progressed to proliferative diabetic retinopathy and received panretinal photocoagulation. Diabetic retinopathy remained stable in all eyes after treatment, and the visual prognosis was good, except in one eye that had macular branch retinal artery occlusion with foveal involvement.

Conclusion. Acute macular edema after pancreas transplantation has a favorable treatment outcome despite rapid progression to proliferative diabetic retinopathy. High pretransplant HbA1c and abrupt blood sugar normalization may be related to the disease course.

Keywords. diabetic retinopathy; hemoglobin A1c; macular edema; pancreas transplantation; soft exudate

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Metformin reduces intrahepatic fibrosis and intrapulmonary shunts in biliary cirrhotic rats

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Abstract

Background. Liver fibrosis causes portal hypertension which dilates collateral vasculature and enhances extra-hepatic angiogenesis including intrapulmonary shunts, which subsequently complicates with hepatopulmonary syndrome. Metformin is an anti-diabetic agent which possesses anti-inflammation and anti-angiogenesis properties. This study evaluated the effect of metformin treatment on liver and lung in a non-diabetic rat model with biliary cirrhosis induced via common bile duct ligation (CBDL).

Methods. CBDL rats were fed with metformin 150 mg/kg/day during the 8th–28th day post operation. The hemodynamic and biochemistry parameters were tested, and blood gas analysis was performed. The liver and lung were dissected for protein analysis and immuno-histochemical stains. Intrapulmonary shunting degree was determined using color microsphere method.

Results. Metformin treatment neither induced obvious hypoglycemic event nor altered hemodynamics in cirrhotic rats. The plasma levels of alanine aminotransferase were significantly reduced by metformin (control vs. metformin: 269 ± 56 vs. 199 ± 21 IU/L, $p = 0.02$). Sirius Red stains and CD-68 stains showed that metformin reduced intrahepatic fibrosis and CD-68-positive macrophages. Metformin did not influence hypoxia and intrapulmonary angiogenesis; however, it significantly reduced intrapulmonary shunts (31.7 ± 10.1 vs. 15.0 ± 6.6%, $p = 0.006$.). Furthermore, metformin reduced the protein expressions of COX-2 and PI3K in liver and COX-1 in lung.

Conclusion. Metformin reduced liver injury and improved hepatic fibrosis in cirrhotic rats. It also attenuated the intrapulmonary shunts. However, the effects of metformin on pulmonary angiogenesis and hypoxia were insignificant.

Keywords. Angiogenesis; Hepatopulmonary syndrome; Liver cirrhosis; Metformin

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Gap between guidelines and clinical practice in heart failure with reduced ejection fraction: Results from TSOC-HFrEF registry

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ABSTRACT

Background. Heart failure (HF) is a global health problem. Guidelines for the management of HF have been established in Western countries and in Taiwan. However, data from the Taiwan Society of Cardiology-Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry showed suboptimal prescription of guideline-recommended medications. We aimed to analyze the reason of non-prescription and clinical outcomes as a result of under-prescription of medications.

Methods. A total of 1509 patients hospitalized for acute HFrEF were recruited in 21 hospitals in Taiwan by the end of October 2014. Prescribed guideline-recommended medications and other relevant clinical parameters were collected and analyzed at discharge and 1 year after index hospitalization.

Results. At discharge, 62% of patients were prescribed with either angiotensin-converting enzyme-inhibitors (ACEI) or angiotensin receptor blockers (ARB); 60% were prescribed with beta-blockers and 49% were prescribed with mineralocorticoid receptor antagonists (MRA). The proportions of patients at ≥ 50% of the target dose for ACEI/ARB, beta-blockers and MRA were 24.4%, 20.6%, 86.2%, respectively. At 1-year follow-up, dosages of ACEI/ARB and MRA were up-titrated in about one-fourth patients, and dosages of beta-blocker were up-titrated in about 40% patients. One-year mortality rate was lowest in patients who received

at least 2 classes of guideline-recommended medications with ≥ 50% of the target dose, and highest in those who received 0 or 1 class of medications.

Conclusion. The TSOC-HFrEF registry demonstrated the under-prescription of guideline-recommended medications and reluctance of physcians to up-titrate medications to target dose. Action plan needs be formulated in order to improve physician's adherence to HF guidelines.

Keywords. Adherence; Beta-blocker; Guidelines; Heart failure; Renin-angiotensin blockade; Taiwan

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Are patients with bladder oversensitivity different from those with urodynamically proven detrusor overactivity in female overactive bladder syndrome?

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ABSTRACT

Background. To determine if there are clinical and urodynamic (UD) differences between female overactive bladder (OAB) patients with bladder oversensitivity (BO) and detrusor overactivity (DO) via a much lower filling rate.

Methods. In total, 205 patients with OAB symptoms were recruited for this study. During filling cystometry, the bladder was filled at a more "physiological" rate of 20 ml/min. All patients underwent a complete urogynecological evaluation including detailed history, physical examination, urinalysis, pad test for quantification of urine leakage, 3-day frequency-volume chart (FVC) documentation, and completion of a UD study.

Results. The overall incidence of BO was 34.2% and that of DO was 65.8%. The first desire to void (FDV) in patients with BO and DO were at filling of 117.47 ± 21.68 ml and 135.23 ± 22.88 ml, respectively ($p < 0.05$). Maximal cystometric capacities (MCC) in patients with BO and DO were recorded at 259.44 ± 33.87 ml and 265.32 ± 44.05 ml ($p > 0.05$). A receiver operating characteristic (ROC) curve was used to find the cut-off values of FDV for sensitivity and specificity in patients diagnosed with DO. Area under the curve (AUC) was 0.702 ($p < 0.005$, 95% confidence interval: 0.626–0.779) if FDV was determined as more than 127 ml. Patients with BO experienced significantly increased daytime urinary frequency and nocturia symptoms (<0.05). Patients with DO had a significantly higher prevalence of urgent urinary incontinence ($p < 0.05$). In this study, a higher FDV and higher body mass index (BMI) were correlating factors for OAB patients with DO after multiple logistic regression analysis.

Conclusion. Patients with BO seemed to be on a different spectrum compared to those with DO and also had different symptom-specific and associative factors. It was also found that FDV could be good predictive indicator for detecting DO at a low filling rate.

Keywords. Bladder oversensitivity; Detrusor overactivity; Filling rate; Overactive bladder; Urgency

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Association of warfarin with congestive heart failure and peripheral artery occlusive disease in hemodialysis patients with atrial fibrillation

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ABSTRACT

Background. The effect of warfarin on the risk of cardiovascular (CV) disease is unknown among chronic hemodialysis patients with atrial fibrillation (HD-AF).

Methods. Population-based propensity score and prescription time-distribution matched cohort study including 6719 HD-AF patients with CHA_2DS_2-VASc score ≥ 2 were divided into warfarin users and nonusers and followed-up for CV events and death.

Results. Warfarin treatment in HD-AF patients with AF preceding HD was associated with higher risks of developing congestive heart failure [hazard ratio (HR) = 1.82, 95% confidence interval (CI) = 1.29–2.58, $p < 0.01$], peripheral artery occlusive disease (HR = 3.42, 95% CI = 1.86–6.31, $p < 0.01$), and aortic valve stenosis (HR = 3.20, 95% CI = 1.02–9.98, $p < 0.05$). Warfarin users were not associated with risks of ischemic or hemorrhagic stroke and all-cause mortality as compared to nonusers.

Conclusion. Warfarin may be associated with vascular calcification, increasing the risks of congestive heart failure and peripheral artery occlusive disease among HD-AF patients.

Keywords. atrial fibrillation; hemodialysis; warfarin

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Apolipoprotein A1 rs5070 A/G polymorphism with stroke subtypes in Taiwan

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ABSTRACT

Background. Apolipoprotein A1 (ApoA1) is a structural protein of high-density lipoprotein cholesterol; ApoA1 is involved in lipid and cholesterol metabolism. This study evaluated the association of ApoA1 polymorphism (rs5070) with different stroke subtypes in Taiwanese individuals.

Methods. A total of 2139 cases, including 614 controls and 708 large artery atherosclerosis (LAA), 377 small-vessel occlusion, and 440 hypertensive intracranial hemorrhage cases, were enrolled in this study. ApoA1 polymorphism was genotyped through polymerase chain reaction amplification and then subjected to mass-assisted laser desorption ionization time-of-flight mass spectrometry using a Bruker SNP genotyping system in the National Center for Genome Medicine (Academia Sinica, Taipei, Taiwan; http://ncgm.sinica.edu.tw/).

Results. The frequency of ApoA1 rs5070 dominant genotype (AA vs. AG + GG) was not significantly different among LAA, small-vessel occlusion, and hypertensive intracranial hemorrhage groups compared with that of the control group. Compared with diabetic patients with the AA allele, those with the AG + GG allele of ApoA1 rs5070 polymorphism showed a 1.58-fold likelihood of developing LAA (odds ratio = 1.58; 95% confidence interval = 1.00–2.42; P = 0.046), but not small-vessel occlusion or hypertensive intracranial hemorrhage. In male diabetic patients, the odds ratio increased to 1.90-fold.

Conclusion. Our findings suggested that genetic polymorphisms of ApoA1 rs5070 A/G may play a role in the susceptibility to LAA among male diabetic patients.

Keywords. apolipoprotein A1; diabetes mellitus; genetics; polymorphism; stroke

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The pattern of failure and predictors of locoregional control in lateralized buccogingival cancer after postoperative radiation therapy

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ABSTRACT

Background. To evaluate the failure pattern and identify predictors of locoregional control in lateralized buccogingival cancer after postoperative radiotherapy (RT) at a single institution.

Methods. We retrospectively reviewed the clinical data of 150 patients with lateralized oral squamous cell carcinoma, including carcinoma of the buccal mucosa, gingiva and retromolar trigone. All patients underwent radical surgery followed by postoperative RT with or without concurrent chemotherapy. We registered planning computer tomography images with images obtained at recurrence and categorized the failure pattern as in-field, marginal, or out-field recurrence.

Results. The median follow-up duration was 47 months (range, 2–131 months). Twenty-eight patients (19%) experienced locoregional failure, including 20 local failure, 5 regional failure and 3 with both. Among the 24 patients who had image studies at recurrence, 15 patients had in-field recurrence, 5 were marginal recurrence and 4 were out-field recurrence. Seven patients (5%) had contralateral neck failure. Four of 5 patients with marginal failure had recurrent tumors in the infratemporal fossa. In multivariate analysis, extracapsular spread and positive or close surgical margin were associated with poor locoregional control.

Conclusion. Local in-field recurrence is the most common failure pattern in lateralized buccogingival cancer after postoperative RT. The infratemporal fossa is a risk area for marginal failure and should be encompassed adequately in the postoperative RT field. Extracapsular spread and positive or close margin are predictors of locoregional control for lateralized oral cancer. Patients exhibiting such adverse features require more aggressive treatment.

Keywords. Adjuvant radiotherapy; Locoregional neoplasm recurrence; Mouth neoplasm

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2015 Guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the Management of Hypertension

Chern-En Chiang [a,*], Tzung-Dau Wang [b], Kwo-Chang Ueng [c], Tsung-Hsien Lin [d], Hung-I Yeh [e], Chung-Yin Chen [f], Yih-Jer Wu [e], Wei-Chuan Tsai [g], Ting-Hsing Chao [g], Chen-Huan Chen [h,i,j,k], Pao-Hsien Chu [l], Chia-Lun Chao [m], Ping-Yen Liu [g], Shih-Hsien Sung [n], Hao-Min Cheng [h,i,j,k], Kang-Ling Wang [a], Yi-Heng Li [g], Fu-Tien Chiang [o,p], Jyh-Hong Chen [g], Wen-Jone Chen [o,q], San-Jou Yeh [r], Shing-Jong Lin [i,j,s]

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ABSTRACT

It has been almost 5 years since the publication of the 2010 hypertension guidelines of the Taiwan Society of Cardiology (TSOC). There is new evidence regarding the management of hypertension, including randomized controlled trials, non-randomized trials, post-hoc analyses, subgroup analyses, retrospective studies, cohort studies, and registries. More recently, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) published joint hypertension guidelines in 2013. The panel members who were appointed to the Eighth Joint National Committee (JNC) also published the 2014 JNC report. Blood pressure (BP) targets have been changed; in particular, such targets have been loosened in high risk patients. The Executive Board members of TSOC and the Taiwan Hypertension Society (THS) aimed to review updated information about the management of hypertension to publish an updated hypertension guideline in Taiwan.

We recognized that hypertension is the most important risk factor for global disease burden. Management of hypertension is especially important in Asia where the prevalence rate grows faster than other parts of the world. In most countries in East Asia, stroke surpassed coronary heart disease (CHD) in causing premature death. A diagnostic algorithm was proposed, emphasizing the importance of home BP monitoring and ambulatory BP monitoring for better detection of night time hypertension, early morning hypertension, white-coat hypertension, and masked hypertension. We disagreed with the ESH/ESH joint hypertension guidelines suggestion to loosen BP targets to <140/90 mmHg for all patients. We strongly disagree with the suggestion by the 2014 JNC report to raise the BP target to <150/90 mmHg for patients between 60-80 years of age. For patients with diabetes, CHD, chronic kidney disease who have proteinuria, and those who are receiving antithrombotic therapy for stroke prevention, we propose BP targets of <130/80 mmHg in our guidelines. BP targets are <140/90 mmHg for all other patient groups, except for patients ≥ 80 years of age in whom a BP target of <150/90 mmHg would be optimal.

For the management of hypertension, we proposed a treatment algorithm, starting with life style modification (LSM) including **S-ABCDE** (**S**odium restriction, **A**lcohol limitation, **B**ody weight reduction, **C**igarette smoke cessation, **D**iet adaptation, and **E**xercise adoption). We emphasized a low-salt strategy instead of a no-salt strategy, and that excessively aggressive sodium restriction to < 2.0 gram/day may be harmful. When drug therapy is considered, a strategy called "**PROCEED**" was suggested (**P**revious experience, **R**isk factors, **O**rgan damage, **C**ontraindications or unfavorable conditions, **E**xpert's or doctor's judgment, **E**xpenses or cost, and **D**elivery and compliance issue). To predict drug effects in lowering BP, we proposed the "Rule of 10" and "Rule of 5". With a standard dose of any one of the 5 major classes of anti-hypertensive agents, one can anticipate approximately a 10-mmHg decrease in systolic BP (SBP) (**Rule of 10**) and a 5-mmHg decrease in diastolic BP (DBP) (**Rule of 5**). When doses of the same drug are doubled, there is only a 2-mmHg incremental decrease in SBP and a 1-mmHg incremental decrease in DBP. Preferably, when 2 drugs with different mechanisms are to be taken together, the decrease in BP is the sum of the decrease of the individual agents (approximately 20 mmHg in SBP and 10 mmHg in DBP). Early combination therapy, especially single-pill combination (SPC), is recommended.

When patient's initial treatment cannot get BP to targeted goals, we have proposed an adjustment algorithm, "**AT GOALs**" (**A**dherence, **T**iming of administration, **G**reater doses, **O**ther classes of drugs, **A**lternative combination or SPC, and **L**SM + **L**aboratory tests). Treatment of hypertension in special

conditions, including treatment of resistant hypertension, hypertension in women, and perioperative management of hypertension, were also mentioned.

The TSOC/THS hypertension guidelines provide the most updated information available in the management of hypertension. The guidelines are not mandatory, and members of the task force fully realize that treatment of hypertension should be individualized to address each patient's circumstances. Ultimately, the decision of the physician decision remains of the utmost importance in hypertension management.

Keywords. Asia; guidelines; hypertension; Taiwan

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適應症 類風濕性關節炎Humira適用於患有中度至重度類風濕性關節炎，並且曾經對一種或超過一種的DMARDs藥物有不適當反應的成人患者，可減輕症狀與徵兆(包括主要臨床反應和臨床緩解)、抑制結構上損害的惡化。Humira 可單獨使用也可以和MTX 或其他DMARDs 藥物併用。 乾癬性關節炎 適用於對疾病緩解型抗風濕藥物無療效之成人活動性與進行性乾癬性關節炎。Humira可單獨使用也可以和MTX或其他DMARDs 藥物併用。僵直性脊椎炎 適用於減輕患有活動性僵直性脊椎炎的患者之症狀與徵兆。克隆氏症 適用於對傳統治療無效之成人中度至重度克隆氏症(CD)，可減輕症狀與徵兆及誘導與維持臨床緩解。Humira亦適用於對iniximab 已經失去療效或無耐受性之成人中度至重度克隆氏症，可減輕症狀與徵兆及誘導與維持臨床緩解。乾癬 對其他全身性治療，包括cyclosporine、MTX 或其他光化學療法無效、有禁忌或無法耐受之中度至重度乾癬成人患者。 潰瘍性結腸炎 Humira 適用於對於皮質類固醇和/或6-mercaptopurine (6-MP) 或azathioprine (AZA) 等傳統治療無效、或對這種療法不耐受或有醫療禁忌之中度至嚴重活動性潰瘍性結腸炎成人患者。腸道貝西氏症Humira適用於治療對傳統治療無效之腸道貝西氏症(Intestinal Behcet's Disease) 患者。化膿性汗腺炎Humira適用於對傳統全身性療法反應不佳的進行性中到重度化膿性汗腺炎(又可稱作acne inversa) 之成人患者。 葡萄膜炎 Humira 適用於治療對類固醇反應不佳，或不適合使用類固醇之成年患者的非感染性中段、後段和全葡萄膜炎。幼年型自發性多關節炎Humira與Methotrexate併用適用於2歲及以上患有活動性幼年型自發性多關節炎，並且曾經對一種或超過一種DMARDs藥物反應不佳之患者。Humira可單獨用於對Methotrexate 無法耐受或不適合持續使用之患者。 小兒克隆氏症 Humira 適用於對皮質類固醇及免疫調節劑(Immunomodulators) 反應不佳之6 歲或大於6 歲中度至重度克隆氏症患者，可減輕症狀與徵兆及誘導與維持臨床緩解。**劑量和給藥**本藥限由醫師使用**禁忌**Humira禁用於已知對Humira或Humira其他賦形劑過敏的病患。 **警語及注意事項** 感染 如同其他TNF拮抗劑，病患應於Humira治療之前、治療期間和之後受到密切的感染監測-包括結核病。於接受Humira治療時發生新感染的病患應受到密切的監測並接受一個完整的診斷評估。如果病患發生嚴重的新感染或敗血症，則應停止投與Humira及開始適當的抗微生物或抗黴菌治療直到感染得到控制。醫師應小心考慮使用Humira於有復發性感染病史或有潛在病況而有可能較易受到感染的病患。 結核病 其他伺機性感染 B型肝炎的復發 **不良反應** 約14%的病患會經歷注射部位反應，是Humira相關臨床試驗上非常常見的不良反應之一。詳細注意事項及其他可能與adalimumab有因果關係的不良反應，請參照仿單資訊。 **包裝** Humira 注射液供應劑型如下：可供注射給藥的無菌溶液，並採用以下包裝配置；並非所有製劑在每一個國家中均已獲得核准： Humira 40 mg/0.4 mL 無菌注射液，以單次使用的預充填式注射器盛裝：• 藥盒內含1 片酒精棉片和1 個塑膠包裝盒，內有1 支預充填式注射器。• 藥盒內含2 片酒精棉片和2 個塑膠包裝盒，其中各有1 支預充填式注射器。• 藥盒內含4 片酒精棉片和4 個塑膠包裝盒，其中各有1 支預充填式注射器。 • 藥盒內含6 片酒精棉片和6 個塑膠包裝盒，其中各有1 支預充填式注射器。 Humira 40 mg/0.4 mL 無菌注射液，以單次使用的預充填式筆型注射器盛裝： • 藥盒內含2 片酒精棉片和1 個塑膠包裝盒，其中有1 支預充填式筆型注射器。• 藥盒內含2 片酒精棉片和2 個塑膠包裝盒，其中各有1 支預充填式筆型注射器。• 藥盒內含4 片酒精棉片和4 個塑膠包裝盒，其中各有1 支預充填式筆型注射器。• 藥盒內含6 片酒精棉片和6 個塑膠包裝盒，其中各有1 支預充填式筆型注射器。 並非所有大小的尺寸均會上市。

藥 商：瑞士商艾伯維藥品有限公司台灣分公司
地 址：台北市民生東路三段49、51號15樓
電 話：(02)25039818
經銷商：衛采製藥股份有限公司
地　址：台北市長安東路一段18號9樓
電　話：(02)25314175

仿單譯自CCDS03320716 July 2016

詳如仿單備載
北市衛藥廣字第104110237 號

衛采製藥股份有限公司
台北市長安東路一段18號9樓
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HyperArc™ high-definition radiotherapy technology is designed to simplify even the most complex non-coplanar SRS treatments. Provide stereotactic radiosurgery and precision radiotherapy for lesions, tumors, and conditions anywhere in the body where radiation treatment is indicated.

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

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*註1：依據實宇藥品資料管理股份有限公司(IQVIA)統計台灣藥業市場資料庫，從2001年至2017年VIAGRA總銷量推估。
*註2：VIAGRA的療效與安全性是由21個為期6個月之隨機取樣，雙盲，安慰劑對照的試驗來評估。給藥病人超過3000名，年齡在19到87歲之間。其療效再經由全世界通用的評估問卷、每日的勃起記錄、勃起功能國際指標(IIEF，一種經過驗證有效的性功能問卷)以及對性伴侶的問卷調查來加以評估。

Viagra
威而鋼®膜衣錠100毫克簡易處方資訊
VIAGRA® Film-Coated Tablets 100 mg
衛署藥輸字第022383號

成分 Sildenafil citrate。 **適應症** 成年男性勃起功能障礙。 **不良反應** 頭痛、潮紅、消化不良、鼻塞、尿道感染、視覺異常、腹瀉、暈眩、起疹、呼吸道感染、背痛、流感症狀、關節痛等。 **禁忌症** VIAGRA不適用於已知對本錠劑中任何成分過敏的患者。有機硝酸鹽類絕對不可以與威而鋼併用。VIAGRA對緊急或長期投予有機硝酸鹽類藥物皆有促進降血壓效果，因此不能與一氧化氮（NO）的供給者、任何型式的有機硝酸鹽或有機亞硝酸鹽類一同服用，無論是固定使用或偶爾使用都是禁忌症的範圍。不可併用之藥物包括有硝化甘油（注射、口服、吸入或貼劑）、isosorbide salts、sodium nitroprusside、amyl nitrite、nicorandil或任何型式之有機硝酸鹽。威而鋼禁止使用於因心血管危險因子而不適合進行性行為的患者。（例如：有嚴重心血管疾病之病患，像患有心衰竭和不穩定型心絞痛患者。）處方使用威而鋼之前，必須考慮到性功能障礙患者可能尚未被診斷出來的心血管疾病。曾發生非動脈炎性前部缺血性視神經病變（NAION）的勃起功能障礙男性患者，不建議使用VIAGRA。VIAGRA使用於下列患者之安全性尚未確立，因此得到進一步資訊之前，禁止使用威而鋼：重度肝功能不全、低血壓（血壓低於90/50 mmHg），高血壓（血壓高於170/110 mmHg）最近曾有中風或心肌梗塞、遺傳退化性視網膜病變如色素性視網膜炎（一小部份的這類患者其視網膜磷酸二酯酵素的基因有異常的現象。） **注意事項** 應該探求完整的病史與進行徹底的身體檢查以診斷勃起功能障礙、判斷可能潛在的病因以及確定適當的治療方式。開始治療勃起功能障礙之前，醫師須考慮到患者的心臟血管功能，包括最近是否有心絞痛發作；因為性行為與心血管危險因子之間，有一定的相關連性。威而鋼有血管擴張的作用，可導致血壓輕微短暫下降，因此會加強了硝酸鹽類降血壓的作用。

*此為簡易處方資訊，完整處方資訊請詳閱仿單
仿單版本：Viagra FCT 100 mg LLD Australia LPD 20151214-2

References: **1.**VIAGRA® package insert (Australia LPD 20151214-2). **2.**Jannini EA, et al. J Sex Med. 2009; 6: 2547-60. **3.**Chen L, et al. Eur Urol. 2015; 68: 674-80. **4.** Nehra A. Mayo Clin Proc. 2009; 84(2): 139–148. **5.**IMS data 2Q2016 **5.** IMS data 2016

北衛廣字第10702002號

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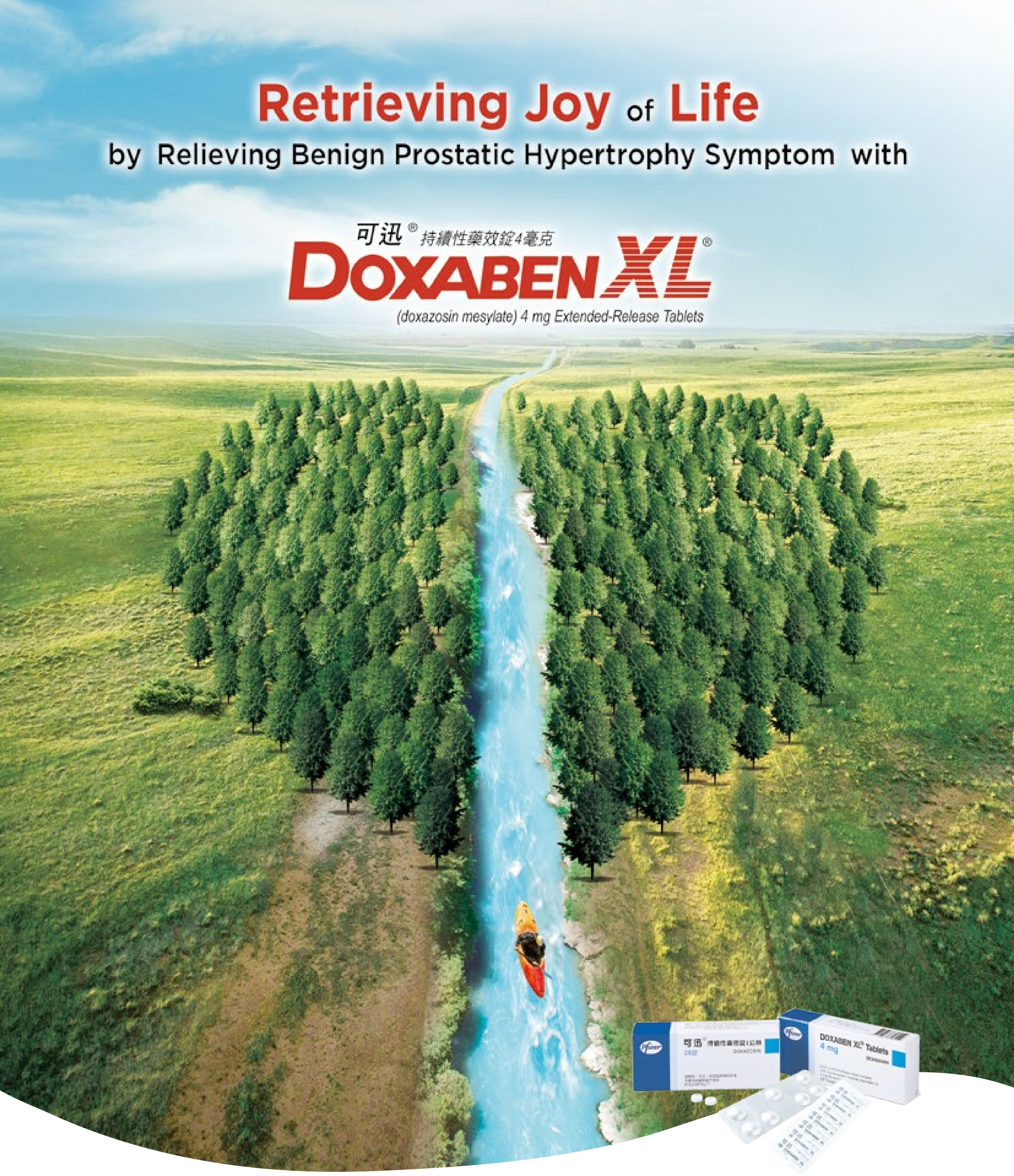
PP-VIA-TWN-0073-201803



[成份] 本錠含有 doxazosin mesylate，相當於 doxazosin 4 毫克。[適應症] 高血壓、良性前列腺肥大。[用法、用量] 本藥需由醫師處方使用。本藥應整錠以足量的液體吞服。患者不可嚼碎、分割或磨碎藥錠，大部分患者以 4 毫克每日一次的劑量即可控制病情。最高建議劑量是 8 毫克每日一次。[禁忌] DoxabenXL 禁用於對 quinazoline、doxazosin 或任何一種非活性成分過敏的患者。[包裝] 4 毫克錠劑，28 錠盒裝。

北市衛藥廣字第106100105號　仿單編號：Doxaben XL LLD CDS 20140924-3

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Xtandi®
安可坦® enzalutamide
軟膠囊40毫克
When his cancer becomes mCRPC[1]
2017 年 9 月 1 日起
給付於化療前 mCRPC 病人*
*相關給付規定請參閱中央健康保險署公告
START Xtandi®
TO EXTEND SURVIVAL[1]
23% reduction in risk of death with XTANDI vs placebo in PREVAIL (HR = 0.77 [95% CI, 0.67-0.88])

癌瑞格® 膜衣錠 40 毫克
品名：癌瑞格®膜衣錠 40毫克
成分: 每錠含有40 mg的regorafenib
許可證字號：衛部藥輸字第 026168 號

適應症與使用方法：
大腸直腸癌:Regorafenib適用於治療先前曾接受下列療法的轉移性大腸直腸癌(mCRC)患者，療法包含fluoropyrimidine-,oxaliplatin- 和 irinotecan-為基礎的化療，和抗血管內皮生長因子(anti-VEGF)等療法；若KRAS為原生型(wild type) 則須接受過抗表皮生長因子受體(anti-EGFR) 療法。
腸胃道間質腫瘤:適用於治療先前曾接受imatinib mesylate與sunitinib malate患者之局部晚期、無法切除或轉移性的腸胃道間質腫瘤患者。
肝細胞癌:STIVARGA 適用於治療曾接受 sorafenib治療的肝細胞癌(HCC)病患。

用法用量：
一個服藥週期為28天，建議劑量為每週期的前21天，每日一次口服160mg STIVARGA (四顆 40 mg藥錠)。持續接受治療直到病況惡化或發生無法接受的毒性。
請於每日同一時間服用STIVARGA。請在食用一份所含熱量不到 600 卡路里及所含脂肪不到30%的低脂餐點後，配水吞服整顆藥錠[請參閱臨床藥理學(12.3)]。請勿為了彌補前一日的劑量，而在一日內服用兩倍劑量的STIVARGA。

禁忌症: 無

北市衛藥廣字第106110293號 L.TW.MKT.11.2017.1519

警語及注意事項:
在臨床試驗中曾出現重度且有時致命的肝中毒性現象[請參閱警語與注意事項(5.1)]。
請在治療之前和治療期間監測肝功能[請參閱警語與注意事項(5.1)]。
藉由肝功能檢測的數值上升程度與肝細胞壞死情形，可了解肝中毒程度，再依據其嚴重程度及持續時間來決定中斷使用STIVARGA後，接下來應該降低藥量或中止使用STIVARGA [請參閱用法用量(2.2)]。
STIVARGA會提高出血機率，涉及中樞神經系統或呼吸道、腸胃道或生殖泌尿道。
STIVARGA曾提高感染、高血壓、心臟缺血與梗塞、皮膚毒性風險。曾觀察到可逆性後腦白質病變症候群、胃腸穿孔或瘻管的案例。
先前未曾在 regorafenib 對傷口癒合的影響上進行過正式的試驗。血管內皮生長因子受體 (VEGFR) 抑制劑 (例如STIVARGA)會妨礙傷口癒合，因此在排定手術的至少前兩週就須停止使用 STIVARGA。手術後根據臨床上傷口癒合情形來判斷是否再度使用STIVARGA。傷口裂開的病患停用STIVARGA。
治療期間及施用最後一劑後2個月內，實施有效避孕。

常見不良反應：
疼痛(包括胃腸疼痛與腹痛)、HFSR、無力/疲累、腹瀉、食慾減退/食量減少、高血壓、感染、發音困難、高膽紅素血症、發燒、黏膜炎、體重減輕、皮疹以及噁心。

更多產品資訊請參詳產品包裝內完整仿單內容 (US 04 / 2017 / TW06)
本藥須由醫師處方使用，使用前應詳閱說明書警語及注意事項

Stivarga®
(regorafenib) tablets

Change Expectations, Start With

保疾伏® 靜脈輸注 20mg,100mg

Nivolumab(基因重組)製劑

人類型PD-1單株抗體

OPDIVO™ (nivolumab)

適應症

無法切除或轉移性黑色素瘤
OPDIVO單一療法或併用ipilimumab適用於治療無法切除或轉移性黑色素瘤病人

非小細胞肺癌
適用於接受含鉑化學治療時或之後疾病惡化的晚期鱗狀非小細胞肺癌(Squamous NSCLC)病人。
適用接受含鉑化學治療時或之後疾病惡化且其腫瘤表現PD-L1 (IHC PD-L1 expression ≥ 5%)的晚期非鱗狀非小細胞肺癌(Non-Squamous NSCLC)病人,病人若具有EGFR或ALK腫瘤基因異常者,則須經EGFR或ALK抑制劑治療後出現疾病惡化現象。

腎細胞癌
適用於先前經抗血管新生療法治療(anti-angiogenic therapy)的晚期腎細胞癌病人。

頭頸部鱗狀細胞癌
適用於接受含鉑化學治療時或之後疾病惡化的復發或轉移性頭頸部鱗狀細胞癌(SCCHN)病人。

典型何杰金氏淋巴瘤
適用於治療接受自體造血幹細胞移植(HSCT)與移植後brentuximab vedotin復發或惡化的典型何杰金氏淋巴瘤病人。

泌尿道上皮癌
適用於治療接受含鉑療法期間或之後惡化的局部晚期無法切除或轉移性泌尿上皮道癌病人。

無法切除的晚期或復發性胃癌
適用於治療先前經兩種或兩種以上化學治療的晚期或復發性胃癌或胃食道癌(Gastroesophageal Junction, GEJ)的病人。

肝細胞癌
適用於先前經sorafenib治療的肝細胞癌(HCC)病人。

【用法】OPDIVO的建議劑量為3 mg/kg連續靜脈輸注60分鐘,每2週一次,直到疾病惡化或出現無法接受之毒性為止。合併使用時,OPDIVO的建議劑量為1 mg/kg靜脈輸注60分鐘後,隨後同一天給予ipilimumab,每3週給予,共4次劑量。後續OPDIVO單一療法的建議劑量為3 mg/kg,連續靜脈輸注60分鐘,每2週一次,直到疾病惡化或出現無法接受之毒性為止。【禁忌症】無。【警語及注意事項】• 使用OPDIVO治療有可能發生定義為需要以皮質類固醇治療且無明顯其他病因之免疫媒介性肺炎(曾通報死亡病例)、免疫媒介性結腸炎、免疫媒介性肝炎、免疫媒介性腎功能不全或腎炎(肌酸酐≥第2級升高)、免疫媒介性皮疹(包括SJS及TEN,曾有致死病例)、免疫媒介性腦炎、免疫媒介性內分泌病變如腦下垂體炎、腎上腺功能不全、自體免疫甲狀腺疾病及第1型糖尿病。• 應監測病人的肺炎、結腸炎、腦下垂體炎及腎上腺功能不全徵兆及症狀,甲狀腺功能及高血糖。應監測病人是否發生皮疹。病人應於治療前及治療期間定期監測肝功能是否異常、是否有血清肌酸酐濃度上升。出現SJS或TEN之徵兆及症狀時,應暫時停用OPDIVO,並將病人轉介至專科進行評估及治療。應評估病人的神經學症狀。應密集追蹤病人移植相關併發症的早期症狀。• 其他免疫媒介性不良反應:在OPDIVO作為單一藥物或併用Ipilimumab治療的臨床試驗中,曾出現下列具臨床意義的免疫媒介性不良反應:心肌炎、橫紋肌溶解症、肌炎、葡萄膜炎、虹膜炎、胰臟炎、臉部及外展神經輕癱(paresis)、髓鞘脫失(demyelination)、風濕性多發性肌痛、自體免疫神經病變、急性多發性神經炎(Guillain-Barré syndrome)、腦下垂體功能低下症、全身發炎反應症候群、胃炎、十二指腸炎、類肉瘤病(sarcoidosis)、組織細胞壞死性淋巴炎(菊地氏病)(Kikuchi lymphadenitis)、運動功能障礙、血管炎及肌無力症。• 輸注反應:接受OPDIVO治療病人其嚴重輸注反應的發生率小於1.0%。• OPVIDO治療後之異體造血幹細胞移植(HSCT)併發症:在使用OPDIVO後進行異體HSCT之病人曾發生併發症,包括致死事件。【懷孕及胚胎毒性】應告知孕婦OPDIVO對胎兒的潛在風險。應告知具有生育能力的婦女在接受OPDIVO治療期間至OPDIVO最後一劑用藥後至少5個月內,需採取有效的避孕措施。【授乳】目前尚不清楚OPDIVO是否會分泌至人體乳汁中。應告知婦女在OPDIVO治療期間停止哺乳。【嚴重不良反應】• 試驗CA209037中為腹痛、低血鈉症、AST增加及脂肪酶增加。• 試驗CA209067中為腹瀉、結腸炎及發熱。• 試驗CA209017中為惡性腫瘤惡化、肺炎、發熱與高血鈣症。• 試驗CA209057中為肺炎、肺栓塞、呼吸困難、肋膜積水及呼吸衰竭。• 試驗CA209025中急性腎臟損傷、肋膜積水、肺炎、腹瀉及高血鈣症。• 試驗CA209141中為肺炎、呼吸困難、呼吸衰竭、呼吸道感染及敗血症。• 試驗CA209205及CA209039中為輸注相關反應、肺炎(pneumonia)、肋膜積水、發熱、皮疹及肺炎(pneumonitis)。• 試驗CA209275中為泌尿道感染、敗血症、腹瀉、小腸阻塞與整體生理健康衰退。• 試驗CA209040中觀察到之毒性數據與其他癌症大致相似,除了較高發生率的轉胺酶及膽紅素升高。【不良反應】• 試驗CA209037中為皮疹。試驗CA209067中為疲倦、皮疹、腹瀉、噁心。試驗CA209017中為呼吸困難、咳嗽、疲倦、與食慾降低。試驗CA209057中為疲倦、肌肉骨骼疼痛、咳嗽、食慾減退和便秘。試驗CA209025中為虛弱狀態、咳嗽、噁心、皮疹、呼吸困難、腹瀉、便秘、食慾降低、背痛及關節痛。試驗CA209141中為咳嗽、呼吸困難。試驗CA209205及CA209039中為皮疹、肌肉骨骼疼痛、搔癢、噁心、關節痛及周邊神經病變。試驗CA209275中為疲倦、肌肉骨骼疼痛、噁心與食慾減退。試驗ONO-4538-12中發生率≥5%的為搔癢、腹瀉、皮疹、及疲倦。

ONO PHARMA TAIWAN
臺北市信義區松高路1號7樓之3
NV-040318-AD-01

【本藥限由醫師使用】
衛部菌疫輸字第001013號 北市衛藥廣字第107040322號
【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】

Bristol-Myers Squibb
臺北市松山區健康路156號4樓
1506TW18PR01982-01

采視明瓶裝注射液
Eylea aflibercept (rch) 40mg/mL solution for intravitreal injection vial
衛署菌疫輸字第000936號
本藥限由醫師使用

剤量與投藥方式
˙ Eylea的建議劑量為2 mg aflibercept (相當於50微升)。

血管新生型(溼性)年齡相關性黃斑部退化病變(wAMD)
˙ Eylea開始治療時為前三個月每個月注射1次，連續注射3次，之後則為每2個月注射1次。患者於治療一年後，若病情需要，建議注射方式為每4~12週接受1次治療。

中央視網膜靜脈阻塞(CRVO)續發黃斑部水腫
˙ 每個月注射1次；樞紐試驗中，前6個月為每個月注射，大部分的進步出現在前3個月。治療必須持續並依據視力和/或解剖學結果延長治療間隔，但目前沒有足夠的證據決定應延長多久的治療間隔。正常情況下，應於注射探訪時做監測。治療間隔延長至完成治療期間，臨床治療醫師應依據病患個別的反應來決定監測時程。

糖尿病黃斑部水腫(DME)所導致的視力損害
˙ Eylea治療開始時為每個月注射1劑，連續注射5劑，之後則為每2個月注射1劑。若視力與解剖結果顯示病患未因持續治療而受益，應停用Eylea。

分支視網膜靜脈阻塞(BRVO)續發黃斑部水腫所導致的視力損害。
˙ 每個月注射1次；樞紐試驗中，前6個月為每個月注射1次，連續注射6次，之後則為每2個月注射一次。大部分的進步出現在前3個月。目前並沒有持續治療超過一年的資料。治療必須持續並依據視力和/或解剖學結果延長治療間隔，但目前沒有足夠的證據決定應延長多久的治療間隔。正常情況下，應於注射探訪時做監測。治療間隔延長至完成治療期間，臨床治療醫師應依據病患個別的反應來決定監測時程。

病理性近視(pathological myopia PM)續發的脈絡膜血管新生(choroidal neovascularization CNV)
˙ 玻璃體內單次注射2 mg aflibercept (0.05mL)，應定期檢查視力以及/或解剖學參數，當視力和影像結果顯示疾病持續、惡化或復發時，可追加注射。注射至同一眼球內的給藥間隔應至少為一個月或以上。在病理性近視續發的脈絡膜血管新生之臨床試驗中·多數的病患在接受治療的一年內，可能只需要一到三次的注射治療，而有些病患可能需要更頻繁的治療。

禁忌：
禁用於對活性物質aflibercept或任何aflibercept賦形劑過敏的病患。
活動性或疑似眼部或眼周感染。活動性重度眼內發炎。

警語與注意事項：
玻璃體內注射相關反應
玻璃體內注射劑，包括使用Eylea，可能與眼內炎、眼內發炎、裂孔性視網膜剝離、視網膜剝離及醫源性創傷型白內障有關。採用適當的無菌注射技術。在注射後該週應監測病患，以在發生感染時及早治療。
玻璃體內注射於60分鐘內，曾觀察到眼內壓升高，包括使用Eylea。對於青光眼控制不佳的病患必須特別注意(當眼內壓≥ 30 mmHg時請勿注射Eylea)。所有病患，都必須監測眼內壓及視神經頭處的灌注，並採用適當的處置。
致免疫原性
與所有治療用蛋白質一樣，使用EYLEA治療的病患可能發生免疫反應。
全身性反應
曾通報玻璃體內注射VEGF抑制劑後發生全身性不良事件，包括非眼球出血及動脈血栓栓塞事件；這些事件可能與VEGF的抑制作用有關且具有理論風險性。
關於6個月內曾有中風、短暫性腦缺血發作或心肌梗塞的CRVO或DME或BRVO或mCNV病患，接受治療的安全性資料有限。應謹慎治療此類病患。
最常見的不良反應(至少5%的EYLEA治療病患)為結膜出血(25.0%)、眼睛疼痛(10.2%)、白內障(7.6%)、眼內壓升高(7.5%)、玻璃體剝離(7.4%)與玻璃體漂浮物(6.9%)。