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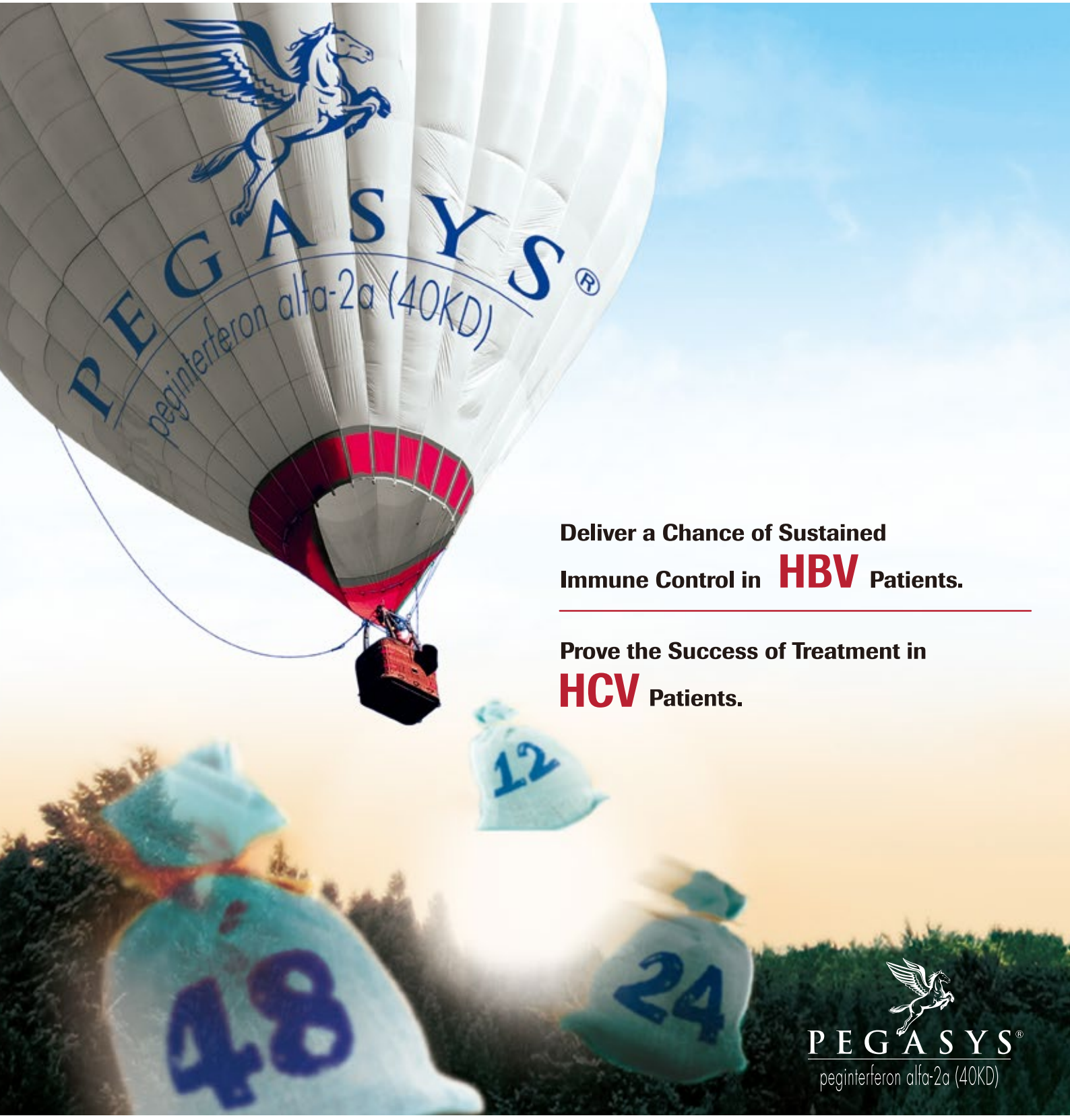


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# 中華醫學會第23屆106年度會員大會

## 暨聯合學術研討會

1

# 2017年榮總台灣聯合大學系統第13期合作研究成果發表會

# Symposium of VGH-UST Joint Research Program

時 間：106年6月10日 09:15~12:30

Time：June 10, 2017 09:15~12:30

地 點：台北國際會議中心 101A 會議室

Place：Conference Room 101A
Taipei International Convention Center

# 2017年榮總台灣聯合大學系統第13期合作研究成果發表會
# Symposium of VGH-UST Joint Research Program

# Identifying the molecular mechanism of hair regeneration alteration in obesity mice by high throughput RNA sequencing and bioinformatics analysis

# 利用次世代高通量基因定序分析來探索肥胖小鼠毛髮再生異常的分子機轉

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**背景：**頭髮在人類社交生活中扮演一個很重要的角色，因為禿頭會使人缺乏自信並顯得蒼老。禿頭的情形會隨著年齡的增長而惡化，其中一個主要的原因為毛囊幹細胞的老化導致再生不良所引起。毛囊是我們器官中少數能終其一生不斷的進行退化與再生的組織，毛囊幹細胞的活化是伴隨著週期性的 b-catenin 的表達所導致。毛囊的再生循環過程主要經由生長期 (anagen)、退化期 (catagen) 到休止期 (telogen) 然後再回到生長期，而毛囊與其周邊之巨環境之間的交互作用使得毛髮的再生與脫落是呈現規律的循環如波浪的型態，而此毛囊再生的訊號也將藉由周邊的巨環境而傳遞至週邊的毛囊並使其活化。這些結果合併之前做的這些研究都暗示著我們，毛囊外的脂肪組織必定存在著更多的循環表現的調控因子來調節幹細胞的再生循環。這個研究的主要目的是要利用肥胖小鼠來當作標的物來探索毛囊外的巨環境如何調控幹細胞的再生循環及老化現象。

**方法：**利用高脂肪的食物來餵食小鼠使其呈現肥胖型態，之後便定期對這些肥胖小鼠及同年齡的正常飲食對照組小鼠進行毛髮剃除，並觀察其毛髮再生週期的現象。在連續觀察一年及一年半之後，分別取這兩組小鼠的皮膚組織以抽取 RNA，利用 RNA-seq 次世代定序來研究其基因表現的變化。

**結果：**在仔細觀察毛髮在生週期時可發現餵食高脂肪食物的小鼠其毛髮再生循環會有明顯的延緩的現象，也就是肥胖小鼠其毛髮的休止期是明顯延長的。而且肥胖小鼠的毛髮密度較正常小鼠稀疏而且也較不容易進入生長期。RNA-seq 次世代定序結果顯示，可促進毛髮進入生長期的因子包括 Leptin 及 Adipoq 在肥胖小鼠上是大量降低的。除此之外，抑制毛髮生長的抑制因子包括 Bmp2 及 Bmp4 則在肥胖小鼠上則是大量表現的。

**結論：**活化因子的大量降低，以及抑制因子的明顯上升是造成肥胖小鼠生長再生週期改變的主要原因，使得肥胖小鼠的毛髮生長期減少且休止期增加。

# Development of rapid detection of circulating cancer cells in patients with colorectal cancer, high throughput chip cells arranged in self-assembly

# 發展高通量細胞排列自組裝晶片快速檢測與計量大腸直腸癌病患之循環腫瘤細胞

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**背景：**大腸直腸癌 The colorectal carcinomas (CRC) 在 10-25％的患者中，在其原發性結腸直腸腫瘤切除時診斷出肝轉移，轉移是由原發腫瘤的惡性細胞傳播引起的多步驟過程。循環癌細胞（Circulating Tumor Cell, CTC）是指從腫瘤上脫落並進入循環系統的癌細胞，通過簡單的血液檢測來發現這些細胞可作為癌症的生物標誌物。近期研究顯示循環腫瘤細胞的多寡與病情的嚴重性和預測有正相關，因此偵測和分析循環腫瘤細胞是非常重要的研究 , 與進一步預防疾病的侵襲和轉移具有高臨床重要性。

**方法：**本計畫收集來自 64 位 CRC 患者的外周血（PB）和腸系膜靜脈血（MVB）用於 CTC 檢測和計數。利用流體的特性，使懸浮細胞液內的細胞受液體流動的拉力而產生單層緊密排列的自組裝排列，細胞螢光直染晶片不須離心即可完成染色。經抗體螢光標定後利用重力和側向拉力的影響，在觀測區域形成二維陣列緊密排列。以可攜帶式數位自動定位影像照相系統觀測循環腫瘤細胞並計算其數量再和病患癌期別的結果對比。而來自外周血的循環未知 miRNA 的檢測和定量將通過 RNA 測序進行分析。進行定量實時 PCR 以進一步確認 miRNA 表達的交替。分析包括 TNM 分期，腫瘤分化，淋巴血管浸潤，神經周圍浸潤，CEA / CA199 生物標記等患者的臨床病理特徵。還將 CTC 和潛在 miRNA 的數量與臨床結果相關聯，包括腫瘤進展（復發，轉移等）。

**結果：**主要成果包括：(1) 實際運用於臨床上的檢測，已經取得台北榮民總醫院合作大腸直腸癌術後病患的血液檢體收到 64 例的臨床血液檢體細胞排列自組裝晶片，找到循環癌細胞並做數量與型態之判斷，提供醫師於臨床作為病患術後之癒後參考。(2) 以細胞螢光直染晶片分別成功三種標定細胞核、循環癌細胞與白血球，不同的螢光標定出的循環腫瘤細胞，不僅降低染色背景值，且縮短染色時間由 90 分鐘下降至 35 分鐘，保留更多的細胞與提升細胞的存活率與健康度。(3) 攜帶式數位自動定位影像照相系統可以拍照出單一細胞解析度約為 7 x 7 pixel，共需要 35 張可拼接為一張觀測孔完整圖，一種螢光檢測需花費 3 分 30 秒左右，三個螢光只需約 10 分鐘即可，僅需 1/4~1/5 耗時於人工觀測的 40~50 分鐘。(4) 共分析 10 個復發和 8 個非復發性 II 期患者的血清 miRNA 譜，血清中 5 種 miRNA 的水平與 II 期 CRC 患者中非復發與復發之間有顯著差異。(5) 在 68 位和 59 位 CRC 患者中分析了 8ml PB 和 MVB 中的 CTC 數，當比較不同的臨床階段時，CTC 細胞數量與臨床階段之間沒有相關性。

**結論：**在本計劃支持下，已經成功開發出預期細胞螢光直染晶片攜帶式數位自動定位影像照相系統，之今後努力的目標為結合細胞螢光直染晶片以及細胞排列自組裝晶片，使得二合一同時具有快速染色以及細胞單層鋪平便於數位自動定位影像照相系統拍攝，統整機制自發且蓬勃地運作的循環癌細胞檢測系統。我們的結果顯示，MVB 中的 CTC 的量高於 PB。而當比較不同的臨床階段時，CTC 細胞的數量與臨床階段之間沒有相關性但 miRNA 與復發與否有關聯性 .。在未來，我們將繼續收集和分析 CRC 患者的 CTC 和 miRNA，並追踪臨床數據和疾病進展。

# The response of skin microbiome as a radiation sensor

# 以微生物體開發輻射治療的感應器

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**背景：**放射療法是一種治療癌症的普遍方法。放射劑量可因癌症的嚴重性而有不同。過度的放射劑量會引起很強的副作用。皮膚細胞對放射的反應與皮膚菌對放射的反應有正相關性。皮膚共生菌生存於人體皮膚表面，這些共生菌跟人一樣接收相同量的輻射，因此測量共生菌對輻射的反應可用來偵測並定量輻射。痤瘡桿菌 (P. acnes) 是人類皮膚上最多的細菌，因此 P. acnes 對放射的反應可能會比其他的放射劑量儀或是放射鏢靶 ( 例如基因標靶 ) 更精準預測放射劑量，以基因改變當作放射反應的標靶可能不專一，因為這些基因的改變可能是因非癌症 ( 例如自體免疫疾病 ) 所引起。

**方法：**評估痤瘡桿菌對輻射的敏感度，檢查氧化 Lsr2 的穩定性和專一性。使用皮膚菌組 (skin microbiome) 對放射的反應製成的快篩試紙 (test strips) 反應出放射劑量。

**結果：**我們已經測出 P. acnes Lsr2 蛋白質某段胜肽 ( DALSLWVDHAR) 可被放射引起氧化作用。氧化的 Lsr2 因此被當作放射治療癌症的標的蛋白。我們也成功的製造出 Lsr2 的單株抗體，且抗體已成功的接合奈米金顆粒，將氧化 Lsr2 抗體與奈米金顆粒製成快篩試紙。

**結論：**利用此試紙，我們已可偵測出頭頸癌病人放射過的皮膚上，其 P. acnes 的 Lsr2 有氧化反應。未來將探討試紙對 P. acnes 的專一性，並比較此試紙與其他方法的敏感度，進而提供醫師在放射治療程中適當的調整放射劑量。

# Investigate the role of immune response in the pathogenesis of Fabry disease and re-evaluation of the routine histopathologic examinations

# 探討免疫反應在法布瑞氏病人的病程及預後中所扮演的角色

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**背景：**法布瑞氏症（Fabry disease）是 X 染色體性聯遺傳的溶酶體儲積症，起因於 α- 半乳糖苷酶 (α-galactosidase, α-GLA) 的基因突變所致。缺乏 α-GLA 酵素活性導致胞內的鞘醣脂 (globotriaosylceramide,Gb3) 無法正常代謝，因而大量堆積在溶酶體內並引發心臟、腎臟及血管的病變。先前我們透過新生兒篩檢發現國人有高比例攜帶心臟變異型法布瑞氏症基因突變點（IVS4+919 G>A）( 男性約 1/1,500)，顯示此一問題為重要的公衛議題。帶有此基因突變點的法布瑞氏症病患，隨著年紀發展肥厚性心肌病變、心臟纖維化、心律不整或心臟衰竭而致死。

方法：我們透過新生兒篩檢及家族族譜分析，追溯其家族中可能發病的成員，若呈現心臟方面的症狀，則利用心電圖、超音波及核磁共振等技術來檢查追蹤。進一步的，我們也以免疫螢光染色或化學染色法做心臟切片的分析，來探討其心臟病變程度與免疫反應。

**結果：**自 2008 年迄今，我們針對 916,383 名新生兒進行法布瑞氏症的篩檢，發現超過 1,439 名個案具有法布瑞氏症基因突變 (GLA 基因 )，其中 1,201 例為 IVS4+919 G>A 突變。經追溯帶突變點位的家屬後共 620 名成人接受心臟超音波檢查，發現超過 40 歲的男性中有 67% 已出現心臟肥大的現象 ( 女性為 32%)。同時透過核磁共振檢查心臟纖維化現象，發現 38.1% 的男性與 16.7% 女性在心臟尚未出現肥厚病症前，就已經有不可逆的心臟纖維化。這些患者中，有 17 例接受心臟病理切片及電子顯微鏡檢查後，皆顯示有明顯的 Gb3 堆積。另外，我們利用患者的心臟切片進一步分析免疫反應，發現法布瑞氏症病人接受酵素補充治療前，其心臟切片有明顯的免疫細胞浸潤，並伴隨有大量的鞘糖脂堆積。我們推論在法布瑞氏症病人中，因為細胞內鞘糖脂長期堆積，導致心臟細胞出現死亡或發炎，並吸引免疫細胞遷移至心臟組織進行清除作用。除此之外，我們也進一步建立更為靈敏的免疫染色方法來檢測心臟病理切片，發現在電子顯微鏡可以偵測到 Gb3 結晶之前，即有明顯的 Gb3 堆積，此結果對於臨床上面的診斷以及用藥時機將有極大幫助。

**結論：**(1) 透過心臟病理切片與其他臨床檢測發現法布瑞氏症的患者在心臟未發生肥大的病理症狀前，就有一部份的患者出現更嚴重的纖維化現象，我們推測病患的免疫細胞可能已經開始浸潤組織。(2) 從患者的心臟病理切片分析發現，法布瑞氏症患者的心臟組織有大量的 Gb3 堆積與免疫細胞浸潤，證實我們先前認為 Gb3 堆積會引發細胞發炎的假說。(3) 經由建立更為靈敏的免疫染色分析方式，我們將能夠偵測到早期 Gb3 堆積的現象，經由與臨床資料的結合，我們希望能夠提供此方式作為早期給藥的參考。

# 2

## 腸內菌與人類疾病

# Gut Microbiota and Human Diseases

時 間：106年6月10日 08:30~12:10

Time：June 10, 2017 08:30~12:10

地 點：台北國際會議中心 101B 會議室

Place：Conference Room 101B
Taipei International Convention Center

# 腸內菌與人類疾病
# Gut Microbiota and Human Diseases

# Gut-liver axis and liver disease

## 「腸 - 肝」軸線與肝臟疾病

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In normal condition, the liver receives a blood supply both from the portal vein and the hepatic artery. Portal venous blood is derived from the mesenteric veins, constitutes about 75% of total blood flow to the liver. The absorbed products of digestion from the intestine enter the liver for further process, then circulating to other organs. On the other hand, the liver secrets conjugated bile acids to the intestine to help digestion and the bile acids absorbed in the terminal ileum to return to the liver. The portal blood from the intestine also contains microbial products. Therefore, the liver is the initial and an important site for filtration of gut-derived products.

Dysregulation of gut-liver axis is commonly observed in patients with non-alcoholic fatty liver disease and/or non-alcoholic steatohepatits, alcoholic liver disease or liver cirrhosis. High fat diets cause dysbiosis and intestinal bacterial overgrowth, contributing increase production of short chain fatty acids, trimethylamine, and ethanol, which lead to steatosis and inflammation in the liver. Dysbiosis further increases intestinal permeability, leading to translocation of micriobial products to the liver. In alcoholic liver disease, ethanol and/or acetaldehyde-induced intestinal inflammation contribute to impaired tight junctions and reduced production of antimicrobial peptides, leading to increased bacterial overgrowth, dysbiosis and bacterial translocation. The migrated bacterial products further deteriorate inflammation in the liver. In liver cirrhosis, impaired intestinal motility, reduced bile flow, altered secretion of immunoglobulin A and antimicrobial molecules lead to intestinal bacterial overgrowth, dysbiosis and impaired intestinal barrier. Large amount of LPS can subsequently enter into the liver and activate immune cells, contributing to inflammation. Bacterial translocation in cirrhosis also leads to infections and other complications of cirrhosis.

Thus, understanding the gut-liver axis and its new signaling pathways may provide new targets for the prevention or treatment of chronic liver injury and liver cirrhosis.

# Microbiota-Gut-Brain axis and neuropsychiatric disorders

## 「菌 - 腦 - 腸」軸線與神經精神疾病

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Microbiota-gut-brain axis is evidenced to play important roles in physical and mental health. Gut microbiota show impacts on brain development and host behavior through a bidirectional communication system between the gut microbiota, the brain the microbiota-gut-brain axis. Psychobiotics, a class of probiotics with psychotropic activities, integrates neural, hormonal, and immunological signaling via gut-brain axis is proved for combating a broad spectrum of complex diseases including mental illness, irritable bowel syndrome (IBS), neurodegenerative disorders and neurodevelopmental disorders. *Lactobacillus plantarum* PS128 was identified and found to normalize depression-like behaviors in early life-stressed mice and to increase locomotor activity in Parkinson's disease-like mice. PS128 reduced the 5-HTP-induced visceral hypersensitivity in a rat model of IBS and reversed the 5-HT(2A/2C) agonist 1-(2, 5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) induced Tourette syndrome-like responses in rats. In the above studies, alteration of the stress hormone, corticosterone, neurotransmitters, dopamine, serotonin and substance P, and neurotrophins, brain derived neurotrophic factor and nerve growth factor, were observed. The results of behavioral tests and neural molecules analysis demonstrate that psychobiotic PS 128 could be a potent alternative for neuropsychiatric disorder.

# The role of gut microbiota and brain function in irritable bowel syndrome

# 腸內菌及大腦功能在腸躁症之角色

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**Abstract**

The clinical importance of irritable bowel syndrome (IBS) is increasing and many gastroenterologists and basic scientists are recently interested in this syndrome. IBS is a prototype of functional gastrointestinal disorders. IBS is very common in general population and the prevalence of IBS is estimated as 10-20%. In the gastroenterological practice, approximately 30% of patients have IBS symptoms. Health-related quality of life (HR-QOL) of IBS patients is substantially disturbed. Having symptoms with IBS results in high health care costs.

The genetic predisposition and influence of environment especially gut micribiota may underlie in the pathogenesis and/or pathophysiology of IBS. This phenomenon, gene x environment interaction together with brain-gut interactions is emerging area to be clarified in IBS research. Research focused on candidate genes of neurotransmitters, cytokines, and growth factors. Among them, some studies but not all studies revealed association between phenotypes of IBS and 5-hydroxytryptamine (5-HT) transporter gene-linked polymorphic region (5-HTTLPR), 5-HT receptor genes, interleukin (IL)-10 gene, IL-6 gene, toll-like receptor-9 gene, cadherin-1 gene or genes relating corticotropin- releasing hormone (CRH). Genome-wide association study reveled that tumor necrosis factor (TNF) SF15 gene, KDEL endoplasmic reticulum protein retention receptor 2 (KDELR2) gene, and glutamate receptor, ionotropic, delta 2 (Grid2) interacting protein (GRID2IP) gene are candidate genes for IBS. Therefore, not only genes coding neurotransmitters but also genes that encode proteins involved in epithelial cell barrier function and the innate immune response to enteric bacteria are associated with development of IBS.

Growing evidence indicated that altered microbiota are present in IBS patients. Earlier studies suggest that microbiota composition is altered by psychosocial stress, psychosocial stress changes host mucosal immune response and mucosal permeability, and that visceral hypersensitivity is induced by this entire process. Gut microbiota and products of gut microbiota especially short chain fatty acid relate to quantified symptoms of healthy controls and IBS patients.

IBS is also a disorder of brain-gut interactions, emotional dysregulation, and illness behaviors. How microbiota play a role in pathophysiology of IBS via dysregulated brain-gut interactions is still unknown. However, brain imaging using positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG) with or without combination of barostat stimulation or electrical stimulation of the colorectum enables us to depict the detailed information of brain-gut interactions. In IBS patients, thalamus, insula, anterior cingulate cortex, amygdala, and brainstem are more activated in response to visceral stimulation than controls. IBS patients also have more desynchronized patterns of EEG and shorter latency of viscerosensory evoked potential. Dysfunction of the prefrontal cortex is also present in IBS patients. Therefore, now it is possible to predict system physiological mechanism of IBS via gut microbiota and brain function.

Further research in gut microbiota and human brain function for the symptom generation in IBS patients is warranted.

# Microbiota in inflammatory bowel disease

## 發炎性腸道疾病和微生物相

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A large number of diverse microbial species reside in the distal gastrointestinal tract, and gut microbiota dysbiosis is associated with diseases ranging from localized gastroenterologic disorders to neurologic, respiratory, metabolic, hepatic, and cardiovascular illnesses. More and more recent studies have demonstrated a dysbiosis in inflammatory bowel disease (IBD) patients. Although the altered microbial profiles did not show any consistent results across these studies, a common feature of reduced microbiota diversity emerged in all patients with IBD.

Several studies using meta-genomics analysis have demonstrated that members of the phylum *Firmicutes* are less abundant in patients with IBD. Among *Firmicutes, Clostridium clusters* XIVa and IV are largely underrepresented in the gut of IBD patients. Accumulating evidence has demonstrated that several environmental factors affect the development and progression IBD, through the induction of intestinal dysbiosis, such as smoking and antibiotics. However, the precise causal relationship between the inflammatory state and a reduction in bacterial diversity remains unclear.

Fecal microbiota transplantation (FMT) involves the transfer of fecal suspension from a healthy donor to the intestinal tract of a recipient, modulating imbalanced gut microbiota and restoring normal diversity and bacterial composition of the intestine. Many studies have revealed that FMT can induce the remission of some IBD patients, especially having the best efficacy in treating patients when first diagnosed. Furthermore, site-directed delivery of molecules showing anti-inflammatory properties using genetically modified (gm)-probiotics shows promise as a new strategy for the prevention and treatment of IBD.

Recent technological advances have provided evidence that gut dysbiosis is one of the triggers and/or mediators of progression of intestinal inflammation in IBD. Bacterial therapy, including FMT and probiotics, has obtained curative efficacy accompanied by an improvement in diversity. Undoubtedly, new discoveries in the field will lead to the development of novel therapeutic approached that aim to restore normal function of the microbiota.

# Gut microbiome in obesity and metabolic disease

# 腸內菌與肥胖及代謝性疾病

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Intestinal microbial community impacts on modulating risk of several chronic diseases, including inflammatory bowel disease, obesity, type 2 diabetes (T2D), cardiovascular disease, and cancer. Changes in intestinal microbial diversity are linked with obese rodents and human beings. An appendix dysbiosis occurs in morbidly obese patients with high insulin-resistance. Obesity is associated with higher *Firmicutes* and lower *Bifidobacterium*, *Bacteroides*-related bacteria and *Lactobacillus*, whereas weight loss achieved by dieting is able to reverse those changes. The microbiota have to be kept at a safe distance in the colon to prevent inflammation, something that is achieved by a dense inner mucus layer that lines the epithelial cells.

Bile acids are signaling molecules that coordinately regulate metabolism and inflammation via the nuclear farnesoid X receptor and the Takeda G protein-coupled receptor 5, which activate transcriptional networks and signaling cascades controlling the expression and activity of genes, and inflammation by acting predominantly in enterohepatic tissues. Gut microbiota plays a central role in the host metabolism of bile acids through deconjugation and dehydroxylation reactions. Unconjugated bile acids significantly altered expression levels of circadian clock genes in the ileum and colon as well as the liver with significant changes to expression of hepatic regulators of circadian rhythm and associated genes. Perturbations of microbial populations in the gut can profoundly alter bile acid profiles that occur across a range of states, including intestinal diseases and extra-intestinal diseases.

Diet plays a significant role in shaping the microbiome. Dietary supplementation with fermentable carbohydrate protects against body weight gain. Fermentation by the resident gut microbiota produces short-chain fatty acids, which act at free fatty acid receptor 2, which is predominantly involved in regulating the effects of fermentable carbohydrate on metabolism and does so, in part, by enhancing peptide YY cell density and release to treat obesity.

Bariatric surgery can teach us about treatment of obesity and metabolic disorders. Emerging evidence indicates a link between the changes in gut microbiota and alterations in both phenotypes and functions of monocytes in patients with obese T2D after Roux-en-Y gastric bypass surgery. In addition, sleeve gastrectomy drives acute and sustained shifts in the gut microbiome in mice, while the shifts are not altered by re-exposure to obesity-associated gut microbiota.

In conclusion, gut microbiome affects host immune and metabolic parameters, with broad implications for human health. Familiarity with these associations will be of tremendous use, especially in obesity and metabolic diseases, to the clinician as well as the patient.

# Gut microbiota in pediatric diseases and health

# 腸道菌叢與兒童健康

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With the advent of advancing culture-free DNA sequencing and bioinformatics technology, we are now able to understand the gut microbiome community with unprecedented precision. The gut microbiota are now expanding their roles in the health and disease status in many fields, including metabolic diseases (diabetes, obesity), cancer (colon cancer and other GI malignancies), liver diseases (fatty liver, cirrhosis), immunologic diseases (allergic diseases), brain-gut disorders (irritable bowel syndrome, IBD, autism, Parkinsonism), and so on.

There are many factors influencing the constitutions of the gut microbiota, including diet, geography, genetic factors, age, and drugs, particularly antibiotics. Currently, the scientists are exploring the different microbiota signature between the disease and health status and aim to manipulate the gut microbiota signature to an optimal condition. Basically, the diversity of the gut microbiota composition can implicate the healthy and diseased status.

The cross-talk among the microbiota and the immune system and the intestinal epithelium is obviously an intriguing and fascinating issue. As a pediatrician, it is interesting to know how the newborns and infants acquire and evolve gut microbiota. The origin of the bacteria colonizing the neonatal gastrointestinal tract is supposed to be affected by mode of delivery, feeding and maternal condition. The neonates may acquire phylum *Proteobacteria, Actinobacteria, Bacteroidetes, and Firmicutes.* These were the major bacteria patterns in infancy. The infants' gut microbiota pattern gradually transit into the adult pattern at about the age of three, when the food intake of the children is similar to that of the adults.

Gut microbiota signature acquired in infancy may predict or incline to the future development of diseases, for example, allergic diseases or metabolic diseases. In the future, people are more focusing on the functions of these gut microbiota. Although people in different geographic area may display different gut microbiota patterns, their gut microbiota may share the approximate functions. With the advent of next generation sequencing technology and the combination with proteomics and metatranscriptomics, a long-term prospective monitoring on the development of diseases and the evolution of gut microbiota will be very helpful to unravel their critical role in the pathogenesis of many diseases and the gut microbiota may become the therapeutic target.

# Diet and gut microbiota

# 飲食與腸道菌叢

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There is considerable enthusiasm around maintaining an optimal gut microbiome in health and in patients with chronic intestinal disease – microbiota are actively involved in pathogenic mechanisms of both injury and healing, plays roles in inducing functional symptoms and have an increasingly-recognised influence on metabolic and cardiovascular health. Unfortunately, whether the microbial changes are cause or effect in many illness settings has not been determined. The idea that the microbiome can be manipulated to prevent and to treat illness is now widely accepted though not always well substantiated. Interventions that have major impact on microbiota, like antibiotics or faecal microbiota transfer, will benefit only a few and are environmentally less responsible or grossly unsophisticated, respectively.

A far more attractive option for manipulating the microbiota is to use diet, since, for example, changes in substrate for the microbial metabolic activity has rapid and potentially profound effects on microbial structure. The limitations we have on utilising diet for such a purpose are not only that it is a challenging therapy to ensure patient compliance, but also the targeted changes are often unknown in their nature. Studies to date have shown that there are certain strategies that can reliably alter microbiota compositional characteristics. For example, a low FODMAP diet will reduce overall bacterial abundance and relative abundance of butyrate-producing bacteria and health-promoting mucous-associated bacteria such as *Akkermansia muciniphila.* Conversely, consuming a modest increase in oligosaccharides in the diet promotes a more 'favourable' microbiota. Diets high in protein and low in fermentable carbohydrates also result in several changes to specific bacterial abundance as does changing micronutrient intake, although there is insufficient reports to know if such changes are consistent across individuals. What is needed is a catalogue of dietary effect that can then be used to design diets to achieve a specific effect on the microbiota structure – if only we knew what structure we wanted! There is a long way to go.

An alternative approach is to use diet to target changes in function of the microbiota by, for example, altering specific metabolic products to modulate the enteric nervous system, achieve an anti-inflammatory effect or minimise injury to the epithelium. This is a very different approach and does not rely on counting bacterial subtypes, but rather considers the microbiota as an organ to be regulated. This approach is used in the low FODMAP diet, where reducing bacterial gas production from carbohydrate fermentation is one of the targets for reducing luminal distension, and, therefore, symptoms of IBS. Fermentable dietary fibre is used to deliver more butyrate to the colonic mucosa for prevention of colorectal cancer and possibly reduction of inflammation in ulcerative colitis. Another example is the reduction of H2S production by microbiota via dietary manipulation as a way of potentially reducing damage to the colonic epithelium in ulcerative colitis.

Hence, diet is a potentially important and powerful tool to alter the gut microbiota to promote health, treat disease and prevent illness. However, our ability to actually achieve this is limited, but the rate of progress in understanding is fast.

# 3

## 智慧醫院2020：自然、友善、高效

## SMART Hospital 2020: A Healing, Friendly and Efficient Environment

**時 間：106年6月10日 09:00~12:00**

**Time：June 10, 2017 09:00~12:00**

**地 點：台北國際會議中心 101C 會議室**

**Place：Conference Room 101C**
**Taipei International Convention Center**

# 智慧醫院2020：自然、友善、高效
# SMART Hospital 2020: A Healing, Friendly and Efficient Environment

# Innovative emergency department patients flow and lean management for improving quality of care

# 創新式急診動線及流程精進醫療品質

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Emergency departments (ED) are chaotic environments in which highly complex and variable patients are sometimes subjected to prolonged ED lengths of stay, increase of complications and overcrowding. To achieve the goal of improving the quality of care and decrease ED overcrowding, the operation of ED should be redesigned.

The innovative ED designations, including integrated structure, fluent process, and strict outcome monitoring, will provide highly quality of care for ED patients, who can enjoy safety and effective medical services. Given the ED structure designation for patient's safety, we should put emphasize on the control of ED entrance, the patient privacy, the effective patient flow, and considerately comfort environment. In regard to ED patients have highly variety of medical diseases, highly risk patients, such as acute myocardial infarction, acute stroke, and severely trauma, should be put on the first priority to treat and dispose promptly by using lean management. Through the continuously monitor quality indicators and audit the results, we can provide medical quality improving.

# Healthcare industry and architectural research of Chinese Mainland and Taiwan in 2017

# 兩岸健康醫養產業與建築研究 2017

**Shih-Chih Chang**
張釋之
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*北京聯華建築上海分公司*

The speaker focused on the development of healthcare industry in Chinese Mainland and Taiwan during the past 20 years, the topic will explore the current healthcare industry and architectural research of Chinese Mainland and Taiwan, which will be supported with explaining the design projects of hospitals and combination of medical and senior care facilities.

Healthcare industry is one of the most important developing fields in 21st century, which involves the medical technology and service, pharmaceutical and biotechnology, medical equipments and facilities, health management, senior care, assurance and finance, those will extend to the future of resident, tourism and education. This speech hopes to interpret the trend of those industries from the perspective of architecture design.

Both Taiwan and Chinese Mainland have become the aged society and have to face the huge challenge of senior care, long-term care and medical problems. The speaker will provide the total solutions to the medical and senior care projects from his design experience, and hope to connect the Taiwanese soft power of international competition in medical field, to propose another point of view for the development of health.

# Promoting the development of intelligent hospitals in Taiwan

## 員林基督教醫院智慧醫療推動經驗分享

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**李國維**

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*員林基督教醫院 院本部*

To provide the most advanced and comprehensive healthcare, Yuanlin Christian Hospital (YCH) developed the first intelligent hospital recently in Asia to comply with patients' demands and the environment rapidly changing. YCH integrated the latest information and communication technologies with HIS to provide comprehensive medical services and improve outpatient efficiency. Deploying various digital signage systems not only makes the hospital's operation management become more efficient and enhance medical quality, but also reduce possibilities of unexpected manual error and manpower.

# Virtual team and real care: The new horizon of future emergency and critical care

# 以跨院際團隊網路協作打造未來式急重症醫療

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The healthcare industry is facing a rapid changing environment, especially in the sector of emergency and critical care. The main problem is human resource crisis. Young physician might choose other easy jobs other than the challenging careers in the emergency department or intensive care units. Lack of on-site supervision and support were the crucial factors. The development of telemedicine and Internet of Things (IoT) may help to resolve this problem.

The development of Tele-Stroke model was one of the successful model for support from the virtual across different hospitals. Progress of intra-arterial thrombectomy (IAT) accelerated the networking between emergency physicians, neurologists and neuro-radiologists from different hospitals. The virtual teams were summoned and through the web communication, physicians could work together to salvage the brain even before the transfer of patients to the tertiary medical centers.

The “eICU” was another famous model for the collaboration between intensivists. In the night time, one intensivist could monitor and supervise patients in several ICUs through the web. That will tremendously reduce the need for duty intensivists in the night time and increase patient safety.

These models were not new, but the truth is that the booming IoT technique fostered the collaboration. The virtual teams were built by emergency physicians or intensivists in different hospitals. The so-called “transfers” would be the results of inter-hospital team approach. The patients actually transferred will be substantially reduced.

The shifting of paradigms will shape the future emergency and critical care. The collaboration of inter-hospital virtual teams will be the common scenarios. For example, the trauma surgeons will involve the care of severe multi-trauma patients even the arrival of patients. They will provide consultation and supervision through the web using the IoT technology. The treatment protocols must be changed significantly. The hardware environment will be modified, too.

To embrace such progresses, we must plan in advance to adopt these changes. The design of ED and ICUs will make a big progress in the near future. The new horizon of emergency and critical care is about to come.

# Patient centered care and patient flow management in a smart hospital: The experiences of Taichung Veterans General Hospital

## 以病人為中心的照護流程智慧設計：臺中榮民總醫院的經驗分享

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Taichung Veterans General Hospital (TCVGH), established in 1982, is a trusted tertiary healthcare provider with over 1,500 beds and 3,600 employees. It is the only public medical center in central Taiwan and handles over 6,500 outpatient visits daily. The provision of holistic care for patients and their family is central to our philosophy of medical care.

However, we face a lot of strenuous challenges, for example, economic stress, emergency department crowding, nurse staffing shortages, limited hospital beds, variability in patient volume, etc. Quality control circles, team resource management, root cause analysis, and lean management are used to appropriately matching the available resources in the system to meet the demand for care and to reduce delays, improve flow and patient safety. The combination of cloud, mobile and digital technologies is also used to improve processes of patient centered care. For example, a novel process has been designed to avoid repeated prescription and medication and to improve medication quality and safety via the Pharma-Cloud system.

At Taichung Veterans General Hospital, we aim to become a leader in the field of smart healthcare. We are well placed to achieve that goal with our use of advanced information technology, a lean management approach, a medical information system with integrated artificial intelligence, innovative medical technology, and a sophisticated system designed to ensure optimal medical quality and patient safety.

# Clinical design officer in hospital of tomorrow: From A to I

# 未來醫院的臨床設計師：從 A 到 I

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In traditional design, the space in hospital will be built first then users have to compromise or adjust their daily work scenarios and service patterns to fit the space. In YongLin X lab, we aim to establish a new model that would take in both medical professionals and patients' requirements from predesign phase in order to create a patient-centered, staff-oriented and technology-advanced medical environment then further drive the brand-new medical culture transformation.

A multidisciplinary team was formed to eliminate the huge communication gap between architects and medical professionals. Then, double diamonds model collocates with user experience and lean process management approaches were used to describe initial concepts which would be further tested and verified by prototyping tools including different scales of mockup and Building Information Modeling(BIM) simulation.

The S.M.A.R.T. Model- that is to fuse Service and Management concepts into design principles then combined with evidence-based Research and emerging Technology to build a user-centered Architecture and healing healthcare environment- has been developed and successfully applied to both brand-new and renovation hospital design projects. Until March 2017, it has conducted in 14 units, such as patient wards, outpatient clinics, intensive care units (ICUs), and so forth, from several hospitals and medical centers in Taiwan.

Current research facets are focused on space configuration, workflow transformation, service design and strategy management and there are three additional cases in process. The research team will put efforts to enlarge scales on change and innovation and pursuit sustainable development in dynamic healing environment design field.

# 4

# 含硼分子在硼中子捕獲腫瘤療法上的應用

# The Application of Boron-containing Compounds in Boron Neutron Capture Therapy (BNCT)

時 間：106年6月10日 08:30~12:00

Time：June 10, 2017 08:30~12:00

地 點：台北國際會議中心 101D 會議室

Place：Conference Room 101D
Taipei International Convention Center

# 含硼分子在硼中子捕獲腫瘤療法上的應用
# The Application of Boron-containing Compounds in Boron Neutron Capture Therapy (BNCT)

# Verification of microdistribution and pharmacokinetics of boron compound for determining CBE factors in BNCT in an experimental animal tumor model

# 以實驗動物腫瘤模式驗證硼化合物之微分布及藥物動力學以確定其於硼中子捕獲治療之化合物生物效應因子

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**Background:** In boron neutron capture therapy (BNCT), the short ranges of the two high-LET products of the boron neutron capture reaction make the microdistribution of boron compound particularly important. Compound biological effect (CBE) is defined as the product of the true relative biological effect of these high-LET particles, and the boron localization factor. CBE factor depends on the pharmacokinetics of boron compound.

**Methods:** The pharmacokinetics, microdistribution and tumor-to-normal tissue boron concentration (BC) ratios following the one-step and two-step infusion of BPA in BNCT were studied. Human oral squamous cell carcinoma SAS cells were implanted subcutaneously into the right forelimbs of BALB/c mice. A 400 mg/kg dose of BPA was administered by intravenous infusion, and then, for the two-step infusion, a low-dose continuous infusion was performed to evaluate the BC in blood, normal tissue, and tumor.

**Results:** Experimental results revealed the T/N BC ratio did not equal the T/B ratio at any time following BPA administration, and the T/B and T/N ratios were related to the time of measurement. The T/N, T/B and N/B ratios can change at any time. Micro-PET images showed that tumor cells in the same transverse section contained different activities of 18F-FBPA-Fr, and the active regions of the tumor may also have contained a low 18F-FBPA-Fr activity. Continuous infusion of BPA at a dose rate of one tenth of that in the first infusion can maintain tumor BC at a level higher than that achieved in groups with non-continuous infusion. A stable and narrow range of N/B ratios can be obtained, which is important for the accurate calculation of boron doses for BNCT.

**Conclusion:** The mode and route of boron drug administration, as well as the distribution of boron within the tumor and normal tissues, can all affect the experimental determination of CBE factor. Boron drug delivery must be optimized if BNCT is to be maximally successful.

# Discussion the pros or cons of Borono-L-Phenylalanine as an anticancer drug in boron neutron capture therapy and try to push it toward precision medicine

# 專論 BPA 作為硼中子捕獲治療藥物的優缺點及推動朝向精準醫療的發展

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The achievement of boron neutron capture therapy (BNCT) relies on the development of boron-containing compounds. Sodium tetraborate (Na2B4O7), boronophenylalanine (BPA), sodium borocaptate (BSH) and decahydrodecaborate (GB-10) have been developed for clinical therapy; however, BPA remains the most important BNCT drug against head-and-neck cancer and brain tumor in this decade.

To provide education and dissemination for academic and clinical studies of BNCT, we revisit the preparation, drug formulation and delivery of BPA in clinical application. Both pros and cons (advantages and disadvantages) of using BPA are evaluated according to viewpoints of chemistry and biology. In terms of chemical issues, the BPA for clinical studies are always boron-10 (10B) enriched and the enriched 10B boric acid is a critical material for not only nuclear industry but BNCT. The 10B-BPA is an amino acid analog with poor solubility in saline. Therefore, the formulation of 10B-BPA infusion solution contains fructose to improve solubility of 10B-BPA through the formation of BPA-fructose complex, which maintains 25 mg BPA in every mL solution. Unfortunately, the presence of fructose in solution may affect the stability of 10B-BPA to eliminate the shelf-life of infusion solution.

In terms of biological issues, BNCT is a cellular level targeting therapy therefore determination of boron concentration in tumor tissue prior to neutron irradiation must be required. The 18F-FBPA, radiopharmaceutical analog of BPA, has been developed for positron emission tomography (PET) in order to evaluate T/N and T/B ratio for 10B-BPA. However, different administration routes and injection doses were employed for 18F-FBPA and 10B-BPA. The comparison of pharmacokinetics and biodistribution between 10B-BPA and 18F-FBPA should be comprehensively studied. Moreover, the BPA could be a substrate and/or inhibitor of L-amino acid transporter 1 (LAT-1). Histopathological inspection of LAT-1 expression in tumor tissue associated with binding affinity between BPA and LAT-1 should be carefully evaluated. We suggest the integration of above-mentioned issues can propel BNCT toward precision medicine.

# The evolution of BNCT drugs: Past, now, and future

# BNCT 藥物的演進：過去、現在、未來

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BNCT is a binary therapy with selective delivery of non-radioactive 10B to cancer cells and thermal neutron beam. When 10B and thermal neutron irradiation are kept distinct, each has only a minor effect on cancer cells; albeit uniting both elements at a tumor releases intense radiation destroy malignant cells. Because the path lengths of the particles are only in the single cell range, approximately 9-10 μm, tumor containing 10B compounds are selectively destroyed by BNCT therapy. The selective tumor targeted boron delivery system is very crucial for effective treatment. Therefore, the key to make BNCT more reliable cancer therapy is the effective delivery and accumulation of boron compounds to the cancer cells, this is the key and aim of the ideal BNCT drugs. The only two BNCT delivery agents currently used in clinical trials are boron-enriched (L)-4-dihydroxy-borylphenylalanine (boronophenylalanine, BPA) and boron-enriched sodium mercaptoundecahydro-closo-dodecaborate (sodium borocaptate, BSH). The high proportion of boron-10 isotope in the BNCT pharmaceutical agents is the key to effective neutron capture therapy; however, boron-10 precursors, as controlled nuclear substances, are very expensive and hard to acquire. By developing novel boron-containing compounds and nano-delivery systems, new generation boron delivery platform for BNCT, with the aim of strengthening the tumor boron uptake efficiency, elevating tumor boron concentration, and further optimizing the drug adsorption in patients for more feasible clinical usage. Herein, I will present the history of BNCT drugs and the evolution of BNCT drugs.

# Current status of boron neutron capture therapy (BNCT) in Japan: Focusing on research and development of boron drugs

# 現今日本硼中子捕獲治療之近況：主要針對含硼藥物之研究及發展方面

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Recently, boron neutron capture therapy (BNCT) has become recognized as an essential therapy for brain cancer, head and necked cancer, and melanoma. BNCT is based on the nuclear capture and fission reactions of the 10B-boron atom with low energy thermal/epithermal neutrons to yield high linear energy transfer a particles and recoiling 7Li nuclei. Because the path length of these particles are approximately 9-10 mm, equal to the dimensions of a single cell, 10B-boron containing cells are selectively destroyed by BNCT. Therefore, BNCT is, in terms of effectiveness and safety, an epoch-making treatment that differs radically from conventional radiotherapy and one that promises to become a fourth option as a treatment to cancer.

In the innovation of elemental technologies making up BNCT, the world's first compact accelerator for BNCT of the cyclotron type was completed in Kyoto University as neutron source in 2009. The establishment of the accelerator instead of a nuclear reactor brought crucial progress to BNCT in Japan and clinical trial of brain tumor started using this apparatus from 2012.

On the other hand, although many kinds of boron compounds, including amino acid, peptide, nucleic acid, liposome, and emulsion etc. have been reported as boron delivery agents f so far, only two compounds, L-p-boronophenylalanine (L-BPA) and dodecaborane thiol (BSH), are clinically used in treatment of cancer with BNCT. L-BPA developed by Mishima et al, has been widely used as an excellent boron delivery agent for BNCT. Because BPA is selectively uptaken into cancer cells via the LAT1 amino acid transporter which is highly expressed only in cancer cells, particularly accumulating in the cell nuclei, and is low in toxicity. Furthermore, 18FBPA with 18F-fluorin introduced into BPA is essentially used as a probe for PET imaging to prepare protocol for treatment of L-BPA/BNCT. In contrast, BSH has no selective affinity to cancer cells, but it has high boron occupancy, low toxicity and permeability to the brain barrier.

In this presentation, I would like to talk about the current situation, problems and future prospect of BNCT in Japan, focusing on boron agents. Also, I would like to express my expectations for collaborative research between Taiwan and Japan.

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## 消化系領域之新影像技術

# 2017 Advanced Image in Gastroenterology

時 間：106年6月10日 08:10~11:50

Time：June 10, 2017 08:10~11:50

地 點：台北國際會議中心 102 會議室

Place：Conference Room 102
Taipei International Convention Center

# 消化系領域之新影像技術
# 2017 Advanced Image in Gastroenterology

# Forward to the future of advanced image in gastroenterology

# 消化系領域進階影像技術之展望

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The rapidly moving technological advances in gastrointestinal endoscopy have enhanced an endoscopist's ability to diagnose and treat lesions in and out of the gastrointestinal tract in recent years. For example: Image-enhanced endoscopy: the improvement in image quality created by the advent of high-definition and magnification endoscopy, alongside image enhancement (narrow band image, I-scan, FICE), produces images of superb quality and detail that empower the endoscopist to identify important lesions that have previously been undetectable. These technique has been widely used during screening and surveillance endoscopy in east countries and can improve the detection rate of early GI tract cancer. In addition, the improvement of spy glass and endoscopic ultrasound technique extends doctor's eye and hand into biliopancreatic system to diagnose and treat the lesions.

The recent commercialized technologies, such as optical coherence tomography and confocal laser endomicroscopy, allow the endoscopist to visualize individual cells on a microscopic level and provide a real time, in vivo histological assessment. In the future, the development of Raman spectroscopy and molecular image may give us an objective and red flag image to diagnosis early cancers and finally achieve the goal of optical histological diagnosis.

# Image-enhanced endoscopy for diagnosing GI tract cancer

# 影像加強型內視鏡診斷消化道早期癌

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Endoscopy has become the important tool for the diagnosis of GI tract neoplasm. In order to make the diagnosis more precise, some methods have been introduced. For example, chromoendoscopy with indigocarmine, crystal violet and Lugol's solution staining have been applied to early detection and accurate diagnosis of cancer or precancerous lesions over esophagus, stomach and colon. Recently, modification of optical source of endoscopy and imaging quality has been developed to observe the mucosal pattern and vascular changes more clearly and characteristically. High-definition endoscopy and magnified endoscopy achieved much improvement. Image-enhanced endoscopy (IEE) such as NBI, FICE, i-Scan, BLI and AFI has been introduced to provide better diagnostic power including high sensitivity or specificity in detecting GI tract neoplasm. Narrow band imaging (NBI) system has been applied for diagnosis of GI tract caner or pre-cancer lesions such as esophageal superficial lesions, gastric cancer, colon polyp or early cancer since 2004. Many studies have demonstrated its good diagnostic accuracy in esophageal squamous cell carcinoma (ESCC), Barrett's esophagus with dysplasia, gastric cancer or intestinal metaplasia and colon polyp. Several endoscopic classification of GI neoplasm basing on NBI with or without magnification had been developed. For example, Sano, NICE and JNET classifications for colon polyp; Inoue's IPCL classification for ESCC and BING criteria for Barrett's esophagus were introduced for clinical application. With innovation of endoscopy technology, the invention of IEE was a milestone in the endoscopic history.

# Advanced direct imaging in biliary tract: Spyglass and cholangioscopy

# 膽道領域之新影像技術：Spyglass and cholangioscopy

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The biliary tree is among the most elusory structures for endoscopic examination. Cholangioscopy can provide direct visualization of the pancreatic and biliary system. The traditional peroral cholangioscopy is limited by cumbersome procedures, time consuming, and the easily broken small-caliber baby scope. Due to the recent advances of endoscopic technology, new types of cholangioscopes have been introduced, which renewed our interests in endoscopic visualization of the biliary tree. The single-operator cholangioscopy (SOC), Spyglass direct visualization system (Boston Scientific), has been introduces since 2007. The main indications for SOC are the evaluation of biliary strictures and lithotripsy for difficult biliary stones. SOC with the SpyGlass system has a reported success rate of higher than 90%. In a recent systematic review, the pooled sensitivity and specificity of SpyGlass visual findings for the diagnosis of malignant biliary strictures were 85% and 83%, respectively, and for SpyGlass-guided biopsies were 60% and 98%, respectively. SOC-guided lithotripsy has a reported success rate of higher than 90%. Nevertheless, the image quality of the first generation SpyGlass was suboptimal, and the image stability was relatively poor because of interference from blood and mucus. The recent introduction of a digital version of the SpyGlass (SpyGlass DS; Boston Scientific) has overcome these limitations. In a recent study, the sensitivity and specificity of SpyGlass DS visual impression for diagnosis of malignancy was 90% and 95.8%, respectively, and for SpyGlass DS-guided biopsies was 85% and 100%, respectively. Cholangioscopy can also be used to facilitate guidewire advancement into selective intrahepatic ducts, for evaluation of pancreas cystic lesions, and used together with probe-based confocal laser endomicroscopy (pCLE) to further enhance the intraductal imaging. In conclusion, the new generation cholangioscopy may provide a more accurate diagnosis of indeterminate biliary strictures, and a high success rate of treatment of difficult stones. The ease of use, improved visualization combined with excellent outcomes and safety profile may lead to more widespread clinical application.

# Appraisal of EUS-guided needle-based confocal laser endomicroscopy in diagnosis of pancreatic lesions

## 內視鏡超音波合併顯微內視鏡診斷胰腺腫瘤之初步探索

**Liang Zhong**

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**Background:** EUS-guided needle-based confocal laser endomicroscopy (EUS-nCLE) has shown prospective in the diagnosis of pancreatic lesions (PLs), but the efficacy of EUS-nCLE have still not evaluated by sufficient studies. We aim to explore the nCLE characteristic of PLs and evaluated its feasibility and reliability of nCLE with a prospective study design.

**Methods:** Patients with PLs were performed EUS-nCLE from October 2016 to March 2017 were prospectively enrolled. We review all nCLE images comparing with the golden standard (surgical section histopathology or FNA cytopathology) and summarized the criteria of different PLs. We made diagnosis of PLs according to the criteria and compared with histo-/cyto-pathological diagnosis to evaluate the sensitivity, specificity, accuracy and complication.

**Results:** In total, 63 patients with PLs were performed EUS-nCLE and surgical section were performed afterward in 32 (51%) patients, and histo-/cyto-pathology were acquired in 53 (84%) patients. EUS-nCLE yielded satisfactory images in all patients. Of the 63 PLs, 24 were cystic, while 23 were solid, and 16 were mixed. According to the pathological diagnosis, pancreatic adenocarcinoma (PDAC) were confirmed in 24 patients, while SCN (16), IPMN (6), MCN (4) and SPT (4) followed. The primary diagnostic criteria of the tumor were summarized. The diagnostic sensitivity, specificity, negative and positive predictive values were analyzed for PDAC and pancreatic cystic lesions (PCLs). nCLE provide high specificity (100%) and positive predictive values (100%) in diagnosis of 3 kinds of cystic lesion. The overall complication rate was 14%, which results from bleeding, pancreatitis and leakage.

**Conclusion:** EUS-nCLE is a promising and supplementary approach in diagnosis of pancreatic lesions, especially PCLs, with high diagnostic accuracy.

# Image-enhanced endoscopy using magnifying endoscopy/ endocytoscopy

## Endocytoscope 診斷消化道早期癌

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Image-enhanced endoscopy (IEE) is a method to emphasize the small blood vessels and minute patterns on the mucosa surface, including NBI, FICE/BLI, i-scan, CLE, AFI, or chromoendoscopy. A number of articles have assessed diagnostic performance of IEE with or without magnification for differentiating non-neoplastic from neoplastic polyps, and the overall diagnostic accuracy mostly achieved more than 90%. In meta-analyses of NBI, i-scan, FICE, AFI, or CLE, these techniques other than AFI could be used with satisfactory diagnostic performance. However the performance levels in the histological prediction by non-experts are not as good as those by experts. Some studies demonstrated training modules or continuous feedback in vivo were beneficial for non-experts to improve their diagnostic performance. In the diagnosis of invasion depth of colorectal cancer, magnifying chromoendoscopy achieved the highest accuracy of 98.8%. Endocytoscopy is a promising development in advanced endoscopic imaging. It is ultrahigh magnifying endoscopy based on contact light microscopy. Using this endoscopy, we could observe the nuclei and cytoplasm in living cells during ongoing endoscopy. The ability to obtain cellular images in real-time has several potential clinical benefits. In this session, I would like to show some preliminary data using IEE and/or magnifying endoscopy/ endosytoscopy.

# Raman spectroscopy in gastrointestinal field

# Raman spectorscopy 於消化道領域之應用

**Lawrence Khek Yu Ho**

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*國立新加坡大學*

Globally white-light endoscopy with biopsy sampling is the gold standard diagnostic modality for esophageal, gastric, and colonic pathologies. However, there is overwhelming evidence to highlight the deficiencies of an approach based predominantly on eyeball visualization. Biopsy sampling is also problematic due in part to excessive sampling and hence attendant cost. Various innovations are currently taking place in the endoscopic domain to aid operators in realtime diagnosis forming, and decision making. These include narrow band imaging which aims to enhance the surface anatomy and vasculature, and confocal laser endomicroscopy which provides real time histological information. However, both of these tools are limited by the skill of the operator and the extensive learning curve associated with their use.

Raman spectroscopy (RS) is a potential platform that aims to provide realtime and objective diagnosis. It enables a fingerprint capture of tissue in relation to the protein, DNA, and lipid content. We have developed the world's one-of-a-kind In-Vivo Molecular Diagnostic System, which is based on Raman spectroscopy – a vibrational technique that enables molecular information to be captured when tissue molecules are agitated by a laser beam. The fibre-optic probe delivers a laser beam and captures the molecular 'fingerprint' of any tissue it comes into contact with – and the information is analyzed in real-time. Cancerous and precancerous tissues have different molecular 'fingerprint' from healthy tissue – so a diagnosis is provided in < 1 second. Proof of effectiveness has been demonstrated in close to 1,000 patients with a diagnostic accuracy of > 90%. Its significance lies in the ability of the technology to allow clinical decision on the spot, thus enabling strategies such as "diagnose & discard", "diagnose and target", "diagnose & resect", "diagnose & mark", and "resect & discard", thus saving time, cost, and minimizing complications by obviating unnecessary biopsy, and limiting resection margin.

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## 精準醫療研討會

# Precision Medicine Conferences

時 間：106年6月10日 08:00~17:30

Time：June 10, 2017 08:00~17:30

地 點：台北國際會議中心 103 會議室

Place：Conference Room 103
Taipei International Convention Center

# 精準醫療研討會
# Precision Medicine Conferences

# Identification of Lysosomal and Extralysosomal Globotriaosylceramide (Gb3) Accumulation in Endomyocardial Biopsies before the Occurrence of Typical Pathological Changes of Fabry Disease

## 偵測溶酶體內外 Gb3 堆積於法布瑞氏症心肌細胞產生病理變化之前

**Dau-Ming Niu**

牛道明

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*臺北榮民總醫院 兒童醫學部*

**Background:** Early initiation of enzyme replacement therapy (ERT) could be effective in stabilizing the progression of Fabry disease (FD), and potentially preventing irreversible organ damage. Certain late-onset cardiac FD treatment guidelines suggest performing an endomyocardial biopsy to confirm typical FD histopathological changes as a prerequisite for the initiation of ERT. However, the sensitivity of routine histological examinations for FD has neither been discussed nor investigated before.

**Objectives:** To evaluate the sensitivity of routine histological examinations with Immunofluorescence (IF) staining of endomyocardial biopsies in FD patients.

**Methods:** IF staining of Globotriaosylceramide (Gb3) and lysosomal-associated membrane protein 1 (LAMP-1) was performed on endomyocardial biopsies of patients who were suspected of Fabry cardiomyopathy, yet had negative or only slight Gb3 accumulation determined by routine histological examinations (Hematoxylin and Eosin [H&E] staining, toluidine blue staining, and electron microscopy examination).

**Results:** The IF staining results revealed that all patients had abundant Gb3 accumulation in their cardiomyocytes, while extralysosomal Gb3 accumulation were found in some patients.

**Conclusion:** Current routine histopathological examinations for FD cardiac biopsies mainly focus on the existence of Gb3 inclusion bodies. However, before the formation of Gb3 inclusion bodies, significant Gb3 had already accumulated in the cardiac tissues. Moreover, the presence of significant extralysosomal Gb3 suggested the irreversible damages of cardiomyocytes might have occurred. We propose that Gb3 IF staining to be performed as a re-evaluation method when no typical FD pathological findings are observed in the biopsies of patients who are highly suspected to have Fabry cardiomyopathy.

# Recent Progresses in Cardiac MRI Study of Fabry Disease in Taiwan

# 台灣法布瑞氏症心臟磁振造影研究發展

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Recently, several studies revealed a much higher prevalence of later onset Fabry mutation, IVS4+919G>A, than previously expected in Taiwanese population. This later-onset FD might present as an important hidden health issue in certain ethnic or demographic populations. However, the natural history of its phenotype has not been systemically investigated, especially the cardiac involvement.

From a cross-sectional analysis of cardiac MRI (CMR) in later-onset FD adults with a mutation of IVS4+919G>A (IVS4-FD), the severity of left ventricular hypertrophy (LVH) increased significantly with age in males, but late gadolinium enhancement was noted in 38.1% of men and 16.7% of women before LVH. Thus, it might be too late to start enzyme replacement therapy after the occurrence of LVH or other significant cardiac manifestations in patients with later-onset FD.

We found that IVS4-FD differed from classical FD in several CMR features: the later onset of LVH, the pattern of asymmetric septal hypertrophy and less-characteristic distribution of LGE. In patients with MWT < 12mm, the chance of positive LGE in CMR is low. Physicians should maintain a high index of suspicion, and order serum enzymatic or genetic tests when a patient presents with unexplained HCM to facilitate an early diagnosis of this treatable, while often underdiagnosed, lysosomal cardiomyopathy in populations with high prevalence of FD.

Therefore, a new quantitative method is necessary to early detect the insidious, ongoing cardiac damage before occurrence of LVH or myocardial fibrosis. A modified Look-Locker inversion recovery (MOLLI) technique was used to measure the native T1 value of the interventricular septum in 18 later-onset FD patients (14 males), who all received endomyocardial biopsies. We found a significant negative correlation between T1 value and histological Gb3 accumulation. We believe that native T1 mapping might be a promising tool to monitor disease progression to ERT treatment response.

# Small Nerve Functional Study of Fabry Disease in Taiwan

# 台灣法布瑞氏症之小神經功能研究

**Ting-Rong Hsu** [a,b], **Yun-An Tsai** [c], **Dau-Ming Niu** [a,b]

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An earlier enzyme replacement therapy implicates a better outcome in the patients with Fabry disease. Small nerve neuropathy has been well documented in patients with Fabry Disease. It is interesting and important to investigate the small nerve function in our specific population of patients with Fabry disease in Taiwan.

From 2008 to 2016, more than 916,383 newborns were screened for Fabry disease by our team. More than 1400 individuals with Fabry mutations were identified. For the 441 newborns with Fabry mutations, 10 children (7 boys and 3 girls) with classical mutations were identified. Six boys (median age: 4.57) were enrolled to identify the early impairment of small fiber neuropathy by sympathetic skin response. To our surprise, 5 children (83%) showed abnormal sympathetic skin response, even when they didn't have any significant symptoms of Fabry disease. The following sympathetic skin response studies for the 4 boys showed still abnormal. The study showed stable in two boys and more decreased amplitude in the other 2 boys. More than 1200 individuals with IVS4 mutations, a large portion of our patients had abnormal SSR and CPT results, even though most of them didn't have any significant clinical s/s for peripheral neuropathy.

Small nerve neuropathy presented early in these children with classic Fabry disease and also the individuals carrying IVS4 mutations in Taiwan.

# Investigate The Role of Immune Response in The Pathogenesis of Fabry Disease and Re-evaluation of The Routine Histopathologic Examinations

## 法布瑞氏症病人心臟組織切片與其免疫反應

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Early initiation of enzyme replacement therapy (ERT) could be effective in stabilizing the disease progression and potentially prevent irreversible organ damages for Fabry disease (FD). However, the sensitivity of the routine histological examinations for FD has never been discussed and investigated. Moreover, if immune response participates in the pathogenesis of FD remains to be explored. We aimed to establish a sensitive detection method specific to globotriaosylceramide (Gb3) accumulation to re-evaluate the sensitivity of routine histological examinations of endomyocardial biopsy of the Type-2 cardiac FD patients, and investigate if there is any correlation of Gb3 accumulation to over-active immune responses. Gb3 immunofluorescent (IF) staining was performed on endomyocardiac biopsies of Type-2 cardiac FD patients who were suspected to have Fabry cardiomyopathy but were negative for Gb3 accumulation or had only scanty Gb3 accumulation by routine histological examinations. All of the suspected patients examined showed abundant Gb3 accumulation in their cardiomyoctes by IF staining. We found that current routine histopathological examinations for Fabry cardiac biopsies were mainly focusing on the existence of Gb3 inclusion body in cardiomyoctes. However, before the formation of Gb3 inclusion body, significant Gb3 had already accumulated in the cardiomyoctes of Fabry patients, accompanied with immune infiltrates. We proposed that Gb3 IF should be undertaken as a re-evaluation method when no typical FD pathological findings were observed in the biopsy of the highly suspected FD patient with cardiomyopathy.

# Renal study of Fabry disease in Taiwan

# 台灣法布瑞氏症的腎臟學研究

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Fabry,s disease is an X-linked lysosomal storage disorder caused by deficiency of the lysosomal hydrolase α-galactosidase A (α-GalA) that renders intra-lysosomal accumulation of globotriaosylceramide (Gb3) in various organ systems. Initially, micro-albuminuria and proteinuria might appear in the teen ages, and progressive renal dysfunction developed thereafter. If not treated with enzyme replacement, most patients deteriorated to end-stage renal disease in their 4th and 5th decades. Consequently, systemic derangements developed as cerebrovascular and cardiovascular dysfunction. Actually, Fabry's disease is a cardiorenal syndrome type 5.

Despite marked advances in patient care and improved overall outlook, it remains obscure regarding annotation of gene variants and the genotype–renal phenotype relations in Fabry's disease. There is still no biomarker to prescribe individualized dosage and ascertain dosage response to the costly enzyme replacement therapy (ERT). There is neither companion diagnostic tools for tailored treatment regimen as ERT only, substrate synthesis reduction combined with ERT, or with the pharmacological chaperone. Moreover, there is also lack of marker to define treatment failure to halt ERT.

We believe the concept of kidney precision medicine by deliberate interpretation of renal biopsies of Fabry's disease, incorporation of technological platforms would create a kidney tissue atlas, define disease subgroups, and identify critical cells, pathways and targets for novel therapies.

# Precision Medicine in Taiwan

# 精準醫學在台灣

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It is widely acknowledged that most currently approved medications cannot have consistent efficacy across all patients, despite the fact that physicians have already made adjustments according to the patients' diagnosis, family history and socio-economic status. To address the variability of efficacy, genetic and biochemical biomarkers were constantly developed to offer more precise stratifications of patients so that each patient subgroup can be precisely treated. In the past, scientists in Taiwan have achieved useful results for precision medicine, such as the use of human leukocyte antigen B*1502 and 5801 haplotypes for indicating post-treatment severe adverse reactions, the clinical associations between the epidermal growth factor receptor mutations and the efficacy of tumor targeting therapy, the germline single nucleotide polymorphisms in the UGT2B28 and GALNT14 genes for guiding the precise treatment of hepatitis B and hepatocellular carcinoma. We will further outline practical directions of precision medicine, leveraging the power of the next generation sequencing technology.

# Neurological complications in Fabry disease

## 法布瑞氏症的神經症狀

**Max J. Hilz**

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In Fabry disease, deficiency of α-galactosidase A results in the accumulation of glycosphingolipids in body fluids and tissues including corneas, blood vessels, kidneys and also structures of the central and peripheral nervous system. Many patients show cardiovascular and cerebrovascular dysfunction. Cerebrovascular dysfunction is particularly associated with a high risk of strokes and of mortality even at a young age. The prevalence and severity of cerebrovascular complications increase with patients'age.

Although ischemic strokes and transient ischemic attacks are the most prevalent types of overt cerebrovascular events in FD, cases of intracerebral hemorrhages, subarachnoid hemorrhage, microbleeds, cerebral venous thrombosis, and cervical carotid dissection have also been reported. To our knowledge, no cases of vertebral dissection or spinal cord infarction have been documented in the literature to date. Although silent infarcts are common events, also among young patients with stroke, there are no reports on the frequency of silent brain infarcts in FD. Aseptic meningitis can occur concomitantly in Fabry patients who have had cerebrovascular complications. One case of prolonged transient global amnesia has been reported in a Fabry patient. Dementia, cognitive impairment, and depression occur in patients with FD although additional studies are needed to establish a direct link to FD.

Clinical data as well as histologic and neurophysiologic studies showed predominantly small fiber dysfunction in patients with Fabry disease. Patients with Fabry disease (FD) characteristically develop peripheral neuropathy at an early age, with pain being a crucial symptom of underlying pathology. From our findings, we concluded that small fiber dysfunction is more prominent than large fiber dysfunction in Fabry patients. Clinically, small fiber dysfunction contributes to recurrent episodes of burning and lancinating pain and paresthesias in the distal extremities. Such episodes can be typically triggered by changes of the environmental temperature, particularly by warming. Moreover, small nerve fiber dysfunction accounts for altered sympathetic and parasympathetic modulation. Sympathetic dysfunction explains the hypohidrosis and a subsequent poor exercise and heat tolerance. However, the diagnosis of pain is challenging due to the heterogeneous and nonspecific symptoms. Practical guidance on the diagnosis and management of pain in FD is needed. To improve treatment outcomes, pain should be diagnosed early in unrecognized or newly identified FD patients. Treatment should include: (a) enzyme replacement therapy controlling the progression of underlying pathology; (b) adjunctive, symptomatic pain management with analgesics for chronic neuropathic and acute nociceptive, and inflammatory or mixed pain; and (c) lifestyle modifications.

# Fabry - a disease of the myocardium. New insights from cardiac MRI

# 心臟 MRI 探討法布瑞氏症心肌病變的新進展

**James C Moon**

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Fabry disease (FD) is caused by mutations in alpha galactosidase resulting in the intra-cellular storage of sphingolipid and alterations in blood and membrane/circulating lipids throughout the body. The consequence is a multisystem disease. Within individual organs, cardiac involvement now is the principle determinant of outcome: from a mortality perspective, FD is a myocardial disease.

The pathophysiological mechanisms by which cardiac mortality and morbidity are caused is now being elucidated by cardiac MRI. CMR can detect multiple processes in the myocardium.

Initially, in 2003, Late gadolinium enhancement was detected – initially in a partially specific pattern affecting the basal inferolateral wall; later more generalised. This is associated with non-response to enzyme therapy and was shown in advanced disease to represent myocardial fibrosis. In 2013, using myocardial T1 mapping, FD was shown to have a low T1, reflecting myocyte storage. This is a strong signal. 85% of LVH positive hearts and >50% of LVH negative subjects have a low T suggesting that the earliest phase of cardiac involvement in FD can now be seen and potentially intervened on (surrogate endpoint). In 2016, a further mapping technique was used T2 mapping, which detects oedema. The LGE "scar" is shown to have a high T2 (another magnetic parameter) which is usually a sign of inflammation/oedema. This links to blood troponin – which was high in 85% of LVH+ subjects. Combined, this suggests that LGE, at least when no thinning present, has an inflammatory component.

A picture therefore emerges: of myocytes that are initially normal, but then develop storage (low T1). This is followed by hypertrophy and, in the basal inferolateral wall, chronic inflammation (high T2, troponin release). There is some gender dimorphism here with females potentially getting the LVH after the inflammation. Later, the LGE becomes more globalised and scarring and thinning may occur leading to systolic heart failure.

Using these pathophysiological insights in a multiparametric approach we should be able to define disease earlier (low T1), potentially intervening to prevent LVH (targeted therapy) or developing new therapies (?anti-inflammation) and risk stratifying better (?LGE extent). More insights are needed – for example why is the inflammation in FD chronic – whereas in other diseases, it is typically transient.

# What are the benefits of starting treatment promptly?

## 即時治療對法布瑞氏症的益處

**Derralynn Hughes**

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It has been proposed that early initiation of enzyme replacement therapy (ERT) may prevent or reduce the progressive organ system involvement observed in Fabry disease. The potential benefits of prompt initiation of ERT with agalsidase alfa on patient outcomes have been examined recently in two post-hoc analyses of data from the Fabry Outcome Survey (FOS). In both analyses, time to first renal or cardiovascular event from ERT start was compared between prompt ERT initiation (within 24 months of diagnosis or symptom onset for the first and second analysis, respectively) versus delayed ERT initiation (> 24 months after diagnosis or symptom onset for the first and second analysis, respectively).

In the first analysis, patients for whom ERT initiation was prompt (n = 934) and delayed (n = 1002) relative to diagnosis were comparable in terms of gender, race, height, weight, glomerular filtration rate, and left ventricular mass index. Mean age at ERT initiation was also similar, but mean age at time of diagnosis for prompt and delayed groups was 40 and 28 years of age, respectively. Median time between diagnosis and ERT onset for prompt and delayed groups was 7 and 94 months, respectively. Prompt ERT initiation was associated with a significant reduction in the risk of renal ($p = 0.0021$), cardiovascular ($p = 0.0002$) and composite ($p = 0.0042$) events relative to delayed ERT initiation.

In the second analysis, patients for whom ERT initiation was prompt (n = 158) and delayed (n = 1262) relative to symptom onset were comparable in terms of mean age at treatment initiation. Mean age at symptom onset was 36 and 18 years of age for the prompt and delayed group, respectively. Mean time between symptom onset and treatment initiation was 15 months in the prompt-initiation and 311 months in the delayed-initiation group. Prompt ERT initiation was associated with a significant reduction in the risk of renal ($p < 0.001$) and cardiovascular ($p < 0.0001$) events relative to delayed ERT.

Results suggest that there may be significant benefits associated with prompt initiation and long-term treatment with agalsidase alfa in patients with Fabry disease.

# Precision Medicine: Genotype/Phenotype Correlations in Fabry Disease

## 精準醫學：法布瑞氏症基因型 / 表現型的相關性

**Robert J. Desnick**
*Icahn School of Medicine at Mount Sinai, New York, USA*

Today medicine is focused on the development and implementation of precision medicine – medicine that is tailored to be "patient-specific" rather than "disease-generic". For Mendelian disorders, efforts are being directed to develop therapeutic strategies that are mutation-specific, thereby customizing treatments to the variability in phenotypic subtype, disease onset, and severity. Such is the case for Fabry disease (FD), an X-linked lysosomal storage disease caused by pathogenic mutations in the α-galactosidase A gene (GLA) that result in the absent or markedly decreased activity of the lysosomal hydrolase, α-galactosidase A (α-GalA), and the progressive accumulation of its glycolipid substrates in fluids and cellular lysosomes throughout the body.

There are two major FD clinical subtypes: the early-onset "Classic" and the "Later-Onset" phenotypes. Males with the Classic phenotype have little or no functional α-GalA enzymatic activity, marked microvascular endothelial glycolipid accumulation, and develop symptoms in childhood or adolescence. In contrast, males with the Later-Onset phenotype have residual α-GalA activity, less substrate accumulation, and typically develop cardiac and/or kidney disease in the third to seventh decades of life. To date, over 870 mutations in the GLA gene have been reported that cause the Classic or Later-Onset phenotypes, or are benign (HGMD; http://www.hgmd.org). Screening patients for FD in cardiac, renal, and stroke clinics, in newborn screening programs, and by clinical exomic/genomic sequencing continue to identify previously reported as well as novel GLA mutations.

In FD, there are strong genotype/phenotype correlations. Thus, the GLA mutation can predict the phenotype, thereby providing information on the specific phenotype, disease severity, and the natural history of the mutation-specific disease, particularly in affected males. Disease manifestations in female heterozygotes are variable due to random X-chromosomal inactivation. Therefore, knowledge of the patient's GLA mutation should more accurately predict treatment strategies based on 1) experience with previously identified patients with a given mutation, 2) greater understanding of the disease pathogenesis, and/or 3) in vitro expression studies of novel missense mutations. Based on such information, the appropriate treatment can be selected and initiated early enough to prevent, and even reverse, disease progression and organ damage. In this way, we can customize treatment and prevention strategies for more effective clinical outcomes.

To facilitate precision medicine for Fabry disease, we recently established the International Fabry Disease Genotype-Phenotype Database (dbFGP), a Fabry disease-specific web-based database that provides information on the phenotypes of GLA gene mutations. The purpose of this database is to provide healthcare providers, patients, and their families with easily accessible and comprehensive information about Fabry disease, genotype/phenotype correlations, and assistance in the diagnosis and medical management of patients and family members with specific GLA mutations. The database consolidates information from peer-reviewed publications, other databases, and data from the diagnostic and clinical evaluations of patients diagnosed and seen at the Mount Sinai International Center for Fabry Disease, as well as expert Fabry disease diagnostic and treatment centers worldwide. The dbFGP invites contributions of Fabry disease genotype-phenotype information from expert physicians, researchers, and diagnosticians.

# Modeling Human Photoreceptor Development and Disease using Gene-edited 3D Retinal Organoids

## 模組化人類感光細胞發育與基因修飾立體 3D 視網膜結構體

**Karl J. Wahlin**

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Retinal degenerative diseases, such retinitis pigmentosa (RP), cause photoreceptor (PR) cell death and blindness. There are no cures and significant gaps exist in our understanding of how PR loss occurs. To address this we have developed genetically modified human induced pluripotent stem cell (iPSC) retinal cell-reporters to investigate pathways promoting retinal differentiation and potentially uncover pathways leading to PR survival. This work bridges three overlapping technologies; (1) iPSCs to generate 3D-differentiated retinas, (2) small molecule chemical screening to identify pathways that increase PR generation, and (3) gene-editing using CRISPR technology to generate retinal reporter iPSCs. To generate 3D retinas we adapted the forced aggregate approach pioneered by Nakano et al (2010) and further optimized this approach to generate retinal cups that form optic vesicles earlier than previously published. We demonstrated that iPSCs can be readily coaxed into 3D retinal cup-like structures with complex laminar morphology and photoreceptor-like cells that display exuberant outgrowth of rod and cone outer segment-like structures. Next, we developed retinal reporters by using the CRISPR/Cas9 system to fluorescently tag the SIX6 (early retina), CRX (early PRs), and cone and rod opsin genes (mature PRs) respectively. Preliminary analysis of small molecule treated SIX6 reporter cells, which recapitulate early retinal expression of SIX6, has enabled us to uncover new insights into early retinal development and could lead to improved ways to advance 3D retinal organoid technology. These new tools offer a potentially robust platform for the study of photoreceptor development, maturation and disease.

# Application of hypoxic culture on mesenchymal stem cells: from bench to bedside

## 缺氧性培養間葉幹細胞：從基礎到臨床應用

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**洪士杰**

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*臺北榮民總醫院 醫學研究部*

Human bone marrow-derived mesenchymal stem cells (MSCs) have emerged as a promising tool for clinical application. Cultivation of MSCs under hypoxic conditions, the normal physiological status of bone marrow, represents a new platform of MSCs expansion for clinical applications. In a long term culture, hypoxia can inhibit senescence, increase the proliferation rate and enhance differentiation potential along the different mesenchymal lineages. Hypoxia also modulates the paracrine effects of MSCs, causing upregulation of various secretable factors, including the vascular endothelial growth factor and IL-6, and thereby enhances wound healing and fracture repair. Hypoxia also plays an important role in mobilization and homing of MSCs, primarily by its ability to induce stromal cell-derived factor-1 expression along with its receptor, CXCR4. After transplantation into ischemic limb, an environment combined of hypoxia and serum deprivation, can lead to apoptosis or cell death, which can be overcome by the hypoxic preconditioning of MSCs.

Recently, we have demonstrated the application of MSCs expanded under hypoxic conditions for treatment of a variety of diseases, including bony defect, tendon healing, osteoarthritis, hindlimb ischemia, graft versus host disease, and acute hepatic failure. We have filed a clinical trial and was approved by Taiwan Food & Drug Admiration (TFDA). In the current project, bone marrow MSCs were isolated from allogenic healthy donors, expanded under hypoxic conditions, and applied for Phase I/IIa study in treating 18 recipients with critical limb ischemia, including placebo, low dose and high dose groups. All patients enrolled tolerated the treatment very well. No treatment-related adverse events were reported. Some patients reported the improvement of skin color, hair and snail in the affected limbs.

# Development of Personalized Treatments for Type 1 Diabetic Patients Utilizing Autologous Cellular Reprogramming Approaches

# 利用自體細胞程式編譯作為糖尿病第一型個人化治療之發展

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**沈家寧**

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*臺北醫學大學 臨床醫學研究所*

Diabetes mellitus is a major public health problem which affects 422 million people worldwide. 10~20% of patients are type 1 diabetes who usually require insulin treatment for survival for the whole life. Type 1 diabetes mellitus is characterized by complete loss of beta-cells due to T-cell mediated autoimmune attacking leading to a deficiency of insulin. The major treatment for patients with type 1 diabetes is insulin injections. However, insulin injections as a medication for treating diabetes are unable to long-termly control blood sugar levels. Instead, islet transplantation is the potential way to sustainably modulate glycemic status. However, the shortage of donor islets and poor islet graft survival limit the potential use of islet transplantation to treat patients with type 1 diabetes. To provide alternative resources for islets (or b cells) to meet current and future needs, in my talk, I will brief the current progress of generating b cells from either induced pluripotent stem cell or direct cell reprogramming. Transplantation of insulin-producing cells derived from induced pluripotent stem cells may be the most promising treatment strategy for diabetic patients with impaired β-cell function. These cells are easily accessible and have been shown to closely mimic endogenous β-cell function in vivo. While the risks of oncogenesis and transplant rejection are still of great concern, my talk will brief the progress and remaining obstacles in induced pluripotent stem cell research. In addition, patients received the allogeneic islet transplantation were still suffering from side effects of the immunosuppressive medications. Hence, the possibility of producing immune-tolerable b-cells from autologous resources would be a key challenge for developing cell-based therapeutics for type 1 diabetic patients. In my talk, I will discuss the possibility of developing cell therapeutic strategies for patients with type 1 diabetes via autologous cell reprogramming.

# Generation of pan-neural induced neural progenitors via direct cell fate conversion technology

## 利用經由細胞直接編譯技術與生產全神經誘導性前驅神經元

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**郭紘志**

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The development and success of pluripotency reprogramming technology have inspired and encouraged researchers to explore the possibility of directly converting somatic cells into other types of somatic cell, so-called direct cell fate conversion. At present, various cell types, including neurons and neural progenitors (NPs), can be directly induced from cells like fibroblasts (FBs). Our studies on the function of hESC-ENP enriched TFs for NP conversion from human FBs have yielded some intriguing findings that promise to significantly enhance our ability to induce neural progenitors from somatic cells through direct cell fate conversion technology. We identified a panel of neural TFs (nTFs), which were highly enriched in hESC-ENPs, whose overexpression can efficiently convert human fibroblasts into expandable multipotent induced ENPs (iENPs) acquiring the common characteristics of NPs, including in vitro self-renewal, NPC gene and marker expression, and the ability to give rise to astrocytes, oligodendrocytes, and functional CNS and PNS neurons upon in vitro and in vivo differentiation. Furthermore, we demonstrated that iENP platform can be used to recapitulate disease pathological features of neurodegenerative diseases. Collectively, our studies demonstrate a novel paradigm for direct conversion of multipotent iENPs from human somatic cells by hESC-ENP enriched neural TFs. This system will allow rapid generation of large quantities of expandable iNP populations with desirable neural differentiation propensities, and facilitate the discovery of novel mechanisms and drugs for neurodegenerative disease treatment and regenerative medicine.

# Development of Cellular Reprogramming and iPSC Technology As Retinal Disease-based Platform: From Bench to Clinic Bedside

# 發展細胞回春與誘導性幹細胞技術作為視網膜疾病平台：從基礎到臨床應用

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**邱士華**

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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.

# Treatment of cerebellar ataxia with mesenchymal stem cells: a phase I/II trial.

## 以異體間充質幹細胞治療小腦萎縮症的臨床經驗

**Oscar Kuang-Sheng Lee**

**李光申**

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*國立陽明大學 臨床醫學研究所 及 臺北市立聯合醫院*

Spinocerebellar ataxias (SCA), are determined rare diseases by the Office of Rare Diseases Research at the National Institutes of Health. SCA causes progressive difficulty with coordination and gait which interferes in performing normal daily functions. SCA patients die from respiratory failure, aspiration pneumonia, or severe infection within 20 years of onset. There are no approved therapeutics for treating SCA (spinocerebellar ataxia). PolyQ SCAs are caused by an extensive CAG sequence repeat which encodes for expanded polyQ residues within the mutated protein. All polyQ SCA patients clinically present limb and gait ataxia because the same ataxia interactome is shared among subgroups. Extensive polyQ in cells, including Purkinje neurons, leads to cell dysfunction and triggers cell apoptosis. Loss of Purkinje cells leads to the symptoms and disease outcomes of SCA. Our pre-clinical research has achieved pre-clinical evidence suggesting adipose tissue-derived mesenchymal stem cell (ADMSC) transplantation ameliorates motor function deterioration of SCA in transgenic mice by rescuing cerebellar Purkinje cells. The infusion of ADMSC into SCA patients may be safe and may demonstrate evidence of ameliorating motor function deterioration by arresting continued loss of Purkinje cells to premature apoptosis caused by oxidative stress from excessive PolyQ expression. Our trial design includes a single ADMSC infusion into patients with 12 months of follow-up. Primary outcome measures for safety include vital signs, clinical lab tests and adverse events. Secondary outcome measures for early evidence of efficacy include changes in the scale for the assessment and rating of ataxia (SARA) score, changes in sensory organization test (SOT) score, changes in adaptation test (ADT) scores and changes in electronystagmogram (ENG). At 10 months, Phase I / II safety and early efficacy data supports the feasibility of using ADMSC for the treatment of SCA.

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# 兒童脊椎畸形矯正手術麻醉新時代研討會
# 暨北區麻醉月會

# New Age of Anesthetic Care for the Pediatric Spinal Deformity

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

**時 間：106年6月10日　　08:30~12:10**
**Time：June 10, 2017　　08:30~12:10**

**地 點：台北國際會議中心 105 會議室**
**Place：Conference Room 105**
**Taipei International Convention Center**

# 兒童脊椎畸形矯正手術麻醉新時代研討會
# 暨北區麻醉月會
# New Age of Anesthetic Care for the Pediatric Spinal Deformity

# Foolish old man moved the mountains : Experience sharing and prospect in the corrective surgery of pediatric spinal deformity

# 愚公移山：兒童脊椎畸形矯正手術的經驗分享及展望

**Shiau-Tzu Tzeng**

**曾效祖**

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*臺北慈濟醫院 骨科*

Pediatric spinal deformity results from multiple conditions including congenital anomalies, neuromuscular disorders, skeletal dysplasia, and developmental disorders (idiopathic). The classification and treatment of these disorders have evolved since surgical treatment was popularized when Harrington distraction instrumentation was introduced. Segmental fixation revolutionized the surgical treatment of these deformities. Pedicle screw-augmented segmental fixation promises once again to shift the standard of surgical therapy.

Treatment of complex pediatric spinal deformities (severe rigid deformities, failed previous surgeries, or congenital disease) is a big challenge to spine surgeons. Various surgical techniques such as combined anterior-posterior correction with supplement halo traction, or spinal osteotomies can be applied according to the disease entity and magnitude of the deformity. Before attempting an osteotomy of the spine for a spinal deformity, sufficient surgical experience and a thorough understanding of the anatomy of the spine and adjacent structures are needed. Besides, a well-organized team with the other departments is essential. In addition to prevent the drawbacks of the above methods, a new strategy (staged posterior correction) was developed. The advantages of staged posterior correction include: no need of halo-gravity traction, avoid anterior release and subsequent pulmonary function deterioration, avoid vigorous manipulation of spinal cord in each surgery, facilitate curve correction, and accommodate the soft tissue and skin. The correction rate is comparable with traditional methods. The most appropriate methods for deformity correction should be chosen and the potential complications should be considered.

Not only has surgical treatment progressed but also the classification of different forms of pediatric deformity continues to evolve. The application of new technologies such as navigation system and 3D printing will change the way to do deformity surgeries. In this talk, the author will share his clinical experiences in the treatment of various pediatric spinal deformities and look forward to the future development of this field.

# The challenges and managements of anesthetic care for the corrective spinal surgery in early onset scoliosis patients

# 麻醉專業在早發性脊柱側彎手術的困難及處置

**Ying-Chou Hsieh**

**謝瀛洲**

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*臺北榮民總醫院 麻醉部*

Early onset scoliosis (EOS) generally means the scoliosis that occurs before the age of ten. These patients may also combine other congenital and complex type of systemic anomalies. For these patients, if the curve angle in the thoracic cage is too large, heart and lung function might be impaired, Some patients might also have tracheal or bronchial stenosis or cartilage hypoplasia, these conditions would make perioperative airway management much more difficult as usual. Coupled with the possibility of spinal cord injury or ischemia during the corrective procedures, anesthetic care for the corrective spinal surgery in EOS patients is a challanging field in pediatric anesthesia since long ago.

Preoperatively, the anesthesiologists need to conduct a detailed assessment of the physical status of the patient; to communicate with the patient and parents for the risk of anesthesia, and to take into account the child's psychological status, then to select the appropriate anesthesia induction method. Intra-operatively, the anesthesiologists need to closely monitor the patient's physiological parameters and adjust the anesthesia maintenance regimen to facilitate the intra-operative neurophysiological monitoring for reducing the incidence of nerve injury. Postoperatively, to provide immediate care, including respiratory care and pain control in the recovery room.

Although the whole corrective surgery is cumbersome and time-consuming, anesthesiologists should continuously communicate with the surgeons and neurological monitoring physicians during the whole procedure to prevent the occurrence of nerve injury in these pediatric patients. In this short speech, we will highlight the keypoints of anesthetic care in these procedures and present our experiences and some interesting cases over the past few years.

# Tumor disappear：A civil case presentation

# 腫瘤消失：最高法院 102 年度台上字第 1611 號民事裁定

**Jiin Ger**

**葛 謹**

*IRB Administration Center, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*

*臺北榮民總醫院 人體試驗委員會行政中心*

甲因腹痛前往 A 醫院，經醫師安排電腦斷層檢查，發現左下腹腔內有（7x8x9 公分）之陰影，攝影報告為：「巨大軟組織腫瘤在左下腹部前方至下面結腸間。」因而安排 2006 年 1 月 18 日中午手術，惟甲在麻醉時休克，尚未手術即轉送 B 醫院救治，仍於同年 2 月 3 日因「缺氧性腦病變合併中樞衰竭死亡」。法醫研究所法醫師病理解剖後出具令人意外之死亡證明書：「未發現腹部有腫瘤。」醫事審議委員會：(1) 建議病人接受剖腹手術探查，尚無判斷錯誤或不當之處。(2) 甲麻醉誘導後 l5 分鐘內即發生心律不整導致休克，原因不明。(3) 麻醉醫師判定甲為 ASA 分類 I 級（健康級），並無疏失。(4) 心臟並無任何危險因子會誘發急性心肌梗塞，健康病人在麻醉中突然發生休克實屬罕見。尚未發現麻醉醫師有疏失之處。刑事部分依「罪刑法定主義」，眾醫師皆不起訴處分，合乎醫理與法理，應予贊同。民事部分卻因法院認為：「麻醉醫師不在現場！」因而被民事法院認定有過失，其中刑事與民事法院心證不同之趨勢值得醫界特別注意。

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## 創新口腔診療簡介

# Introduction to Innovative Oral Diagnosis and Treatment

時 間：106年6月10日 08:30~12:00

Time：June 10, 2017 08:30~12:00

地 點：台北國際會議中心 201F 會議室

Place：Conference Room 201F
Taipei International Convention Center

# 創新口腔診療簡介

# Introduction to Innovative Oral Diagnosis and Treatment

# Biophotonic technology for elderly diseases diagnosis

# 用光看穿高齡疾病

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Official statistics showing an increase in Taiwan's 65-and-over population indicate that the nation is on course to go from being an "aging society" to an "aged society." With an increase in the population of elderly citizens and a rising life expectancy, it was inevitable that Taiwan will be defined as aged. Recently, biophotonic techniques have been proposed as real-time, noninvasive and nonradiative systems for biomedical applications. These optical systems are used by scientists for research and by clinicians for disease diagnosis and treatment. Not only the structural information but also the functional changes of human tissues can be measured based on the optical detection. The topics of biophotonic research include optical diagnostics and therapeutics, biomedical imaging modalities, near-infrared spectroscopy, optical coherence tomography, neurophotonics, optogenetics, tissue optics, and nano-photonics for biomedical applications. Recently, translational medicine and precision medicine are two emerging approach for clinical researches. Biophotonic instruments and devices can provide the different solutions for the issues because their own advantages. Therefore, the bench-to-bedside optical systems interest the interdisciplinary research from optical engineering to medical diagnosis and therapy. Because of the compact design and cost-effective products of optical devices, the biophotonic instruments are quite attractive for clinician. Currently, the goal of biomedical optical imaging lab (BOIL) is to develop the biomedical optical imaging methods for clinical diagnosis and home-care purpose. In this presentation, the recent works of BOIL will be demonstrated with several projects that include optical neuroimaging, wearable devices, skin characterization, ICU applications, surgery navigation system, and the several topics of aging-associated diseases diagnosis.

# Application of optical coherence tomography (OCT) in digital impression in dentistry

# 應用光學同調斷層掃描於牙科數位建模

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Dental impression is an irreplaceable step for making precise dental prostheses, especially for fixed prosthodontics. In modern dentistry, digital impression technique has drawn much more attention than traditional one. Several commercial digital impression systems were launched and demonstrated pretty good results in making impression for crown and bridge. However, digital impression technique, just like traditional method, still has to do gingival retraction for subgingival margins before dentist can make a qualified impression. Gingiva retraction is considered a time consuming and undesirable step both for dentist and patient, since it may cause patient discomfort, gum laceration, bleeding, inflammation or even gingival recession and possibly jeopardize esthetics. Thus, exemption of gingival retraction is an important issue in improving clinical dental practice.

Unlike current dental digital impression techniques which using visible light source to scan tissue, the Optical Coherence Tomography (OCT) uses infrared light as light source, which has the ability to penetrate certain depths of tissues and provide 3D images of gingiva and underneath hard tissue or calculus. Previously we have shown that OCT could be used as an adjunctive tool to exam initial tooth demineralization, secondary caries, and tooth crack, and to locate subgingival calculus by separating gingiva from tooth in the captured images. Since low dosage, transient infrared light radiation is harmless to human body, OCT certainly shall benefit the pregnant women and children by reducing the risk of x-rays radiation exposure during routine dental checkup.

However, the scan images from OCT are usually distorted due to the disparity of refractive index from different tissues. By system calibration and data processing through certain algorithms, now we are able to transfer OCT images to reconstruct 3D models for dental applications. Comparing to the commercial impression system (Carestream), the OCT prototype that we built demonstrated a comparable result with a precision from 28 to 34 μm, which denoted that OCT has a great potential to replace traditional and digital impression techniques in the future.

# The cutting edge and forward path of 3D printing in dentistry

# 3D 列印在牙科領域上之前瞻應用及未來發展

**Yi-Wen Evin Chen**

**陳怡文**

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In all medical related fields, dental applications are considered as the field which is highly promising to adopt 3D printing, as known as additive manufacturing. It is also a part of digital dental field and has been brought dramatic attention in the dentistry. In applications from orthopaedics to implantology and dental technology, the huge amount of design and manufacturing freedom provided by industrial 3D printing processes enables products to be customized and digitized for individual patients. With advances in 3D imaging and modelling technologies such as computed tomography (CT), cone beam computed tomography (CBCT) and intraoral scanning, and with the history of the use of computer-aided design/manufacturing (CAD/CAM) technologies in dentistry, the benefits of adopting 3D printing increased. Uses of 3D printing include the production of drill guides for dental implants, the production of physical models for prosthodontics, orthodontics and surgery, the manufacture of dental, craniomaxillofacial and orthopaedic implants, and the fabrication of copings and frameworks for implant and dental restorations are all implemented in dentistry world widely. In order to deliver advanced and affordable 3D printed medical care including biomedical devices, implants and therapeutics to improve the dentistry quality, the topics of clinical applications, medical images, regenerative medicine, 3D printing fabrication process, standard operation procedure, and regulations will be included in this presentation. The overall introduction of China Medical University 3D Printing Medical Research Center will be included as well. In addition, several clinical cases will be demonstrated in this talk to express the advantages of 3D printing. Last, the research of 3D regeneration medicine and frontier studies will be shared in this talk.

# Metal additive manufacturing for medical applications

# 金屬積層製造於醫材應用

**De-Yao Lin**

**林得耀**

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*工業技術研究院 雷射中心*

Additive Manufacturing (AM) is one of the most promising techniques in recent years. Because the material properties made by AM is not similar to those by the traditional Rapid Prototype (RP) technique. The accuracy, density, and strength of AM product are much better than those of traditional casting product, and can be really used as the functional components for the industry application. So ASTM had named it as Additive Manufacturing to discriminate traditional RP technique in 2009.

Selective laser melting (SLM) is a useful metal Additive Manufacturing (AM) method that differs from traditional manufacturing processes. In SLM process, metal powders are melted to the liquid state by laser irradiation in a local area. A free-form part can be manufactured from these accumulated local areas by controlling scanning route of laser in every slicing layer. Therefore, users can obtain product with complex geometry shape using SLM process. It could achieve different requirements for medical products such as implants, surgical Instruments, and dental prostheses.

However, many people in Taiwan still know nothing about the properties of AM design and manufacturing. The main purpose of this Presentation is to introduce the medical AM applications. We hope it can help people who interest in the medical application can understand how medical techniques change through using additive manufacturing.

# Digital manufacturing of ceramic dental restoration by CAD/CAM and three dimensional printing

# 陶瓷義齒數位製造：CAD/CAM 與三維列印

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Conventional fabrication process of dental crown is to take an impression of an intraoral abutment, make a stone model as a replica of the abutment, create a wax pattern manually and followed by casting. This process spends times and the quality depends on the experience of dental technician. Therefore, the dental CAD/CAM system was proposed to instead of conventional method in the early of 1970s. First step of dental CAD/CAM system is to obtain a digital impression by an intraoral digitizer to scan the intraoral abutment. Secondly, the crown model can be designed virtually by CAD according to the captured digital data. Finally, the physical crown can be fabricated by CAM system.

Alumina, zirconia and alumina-zirconia have been applied in CAD/CAM system but the most attract material is yttrium stabilized tetragonal zirconia polycrystalline (YTZP) because it has advantage of high fracture toughness, aesthetic and biocompatibility. There are two types of zirconia block for dental CAD/CAM application. One application is the full sintered high dense block and another is the partially sintered weak dense block. The advantage of former application is that no shrinkage involved resulting in a superior fit, but the disadvantage is the inferior machinability causing heavier wear on machining tool. Easy machinability is the major advantage of latter application. However, dimensional adjustment of CAD dental model is essential because post-sintering process induces the extensive shrinkage.

The three-dimensional slurry printing (3DSP) is expected to instead of CAD/CAM for fabrication of zirconia dental restoration. The most attractive advantages of the 3DSP are that the slurry can be recyclely used and many different models can be fabricated in one fabrication cycle. However, the severe volume shrinkage needs to be overcome before it is used in dental laboratory. The 3DSP has advantages of low cost, high fabrication speed and reusable material. However, the mechanical property and accuracy of 3DSP product are the major concerns and required to comparable with CAD/CAM results. This study aims to compare the mechanical properties and accuracy of sintered dental single crown that are made by CAD/CAM system and 3DSP respectively. The composition and sintering parameter will be also presented.

# Materials and applications of 3D printing in dentistry

# 牙科三維列印的材料與應用

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In recent years, 3D printing kept drawing more and more attentions. In IDS (International Dental Show) 2017, the 3D printing products for dental applications became the one of the largest sectors in the exhibition. For different dental applications, the accuracy requirements of the 3D-printed products can vary a lot. For example, a 3D-printed dental model for prosthodontics requires very high accuracy, while a dental model for aligner orthodontics can be more tolerate in accuracy. Therefore, not every 3D printer can meet the requirements of dental applications. The accuracy of a 3D- printed product can be affected by many factors. A good example is that a 3D printer based on DLP or SLA technology has generally better accuracy and resolution than a FDM 3D printer. In this talk, factors that affect the accuracy of a 3D-printed product from a DLP 3D printer will be reviewed. In addition, our spin-off company, Enlighten Digital Dental Materials, which specialized in dental 3D printing materials, will also be introduced.

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# 口腔頭頸癌卓越研究

# Translation Medicine Research in Oral Cancer

時 間：106年6月10日 13:30~17:30

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Taipei International Convention Center

# 口腔頭頸癌卓越研究
# Translation Medicine Research in Oral Cancer

# ASB6 promotes the formation or enrichment of head and neck cancer-initiating cells

# ASB6 在頭頸癌幹細胞形成的角色

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**Background:** Despite the proceeding in cancer management, recurrence or relapse nonetheless occurs, resulting in disease progress and reduced prognosis. Poor survival is closely associated with the subpopulation, termed cancer-initiating cells (CICs), that are responsible for initiation or expansion of tumor, resembling stem cell population. CICs are identified in a variety of cancers, and studies have shown that the mechanism exploited for CIC development are cancer type-specific. In head and neck (HN) cancers, we previously performed a systemic analysis and discovered that the E3 ubiquitin ligase ASB6 is increased in normal human oral keratinocytes treated with the major component of betel nut, and is significantly up-regulated in HN cancer cell lines. We also found that HN cancer patients with high ASB6 expression in their cancer tissue are relatively poor in overall survival. Since both cancer formation and poor prognosis are associated with CICs, in this study we aim to determine whether ASB6 indeed has a role in promoting HN CICs development.

**Methods:** To determine whether ASB6 promotes the stemness of HN cancer cells, we established HN cancer cell lines either with knockdown of ASB6 or stably overexpressing human ASB6. The stem cell phenotypes, including the expression of stem cell markers (such as CD44, memGrp78, Oct-4, or Nanog) and the ability of tumor sphere formation, of these cells were then examined by using multicolor flow cytometry, western blot, and colony formation assay.

**Results:** We showed that several stemness-associated markers were preferentially up-regulated in cells overexpressing ASB6. The potential to form tumor sphere was greatly improved following ASB6 overexpression. In contrast, knockdown of ASB6 significantly down-regulates these stem cell phenotypes. Importantly, mice with tail vein-injected ASB6-overexpressing cells were found with more tumor nodules in lung, indicating that these cells exhibit a superior ability to metastasize.

**Conclusion:** ASB6 is likely to have a role in the development of HN CICs and thereby contribute to poor overall survival of HN cancer patients. Further investigation of the mechanism by which ASB6 promote CIC phenotype may provide insights into how HN CICs can be more effectively targeted, ultimately leading to the development of better cancer therapies.

# Metabolic regulations during head and neck tumorigenesis

# 頭頸腫瘤生成之代謝調節

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**Background:** Head and neck squamous cell carcinoma (HNSCC) is one of the most prevalent neoplasms worldwide. Potent dietary carcinogens including areca nut chewing, tobacco smoking and alcohol consumption are considered as key contributors for neoplastic transformation of HNSCCs. The importance of environmental challenges including oncogenic viral infection and systemic metabolism imbalance linking to development of various cancers have also been emphasized based on numerous preclinical and epidemiological studies. In addition to external metabolic inputs, owing to their great demand of energy and biomolecules for cell growth, cancer cells exhibited unique internal metabolic signature with increased glucose uptake, upregulated glycolytic and de novo lipogenic activity in accompany with impaired oxidative phosphorylation (OxPhos) compared to their normal counterparts.

**Methods:** Recent findings have demonstrated that manipulations of either intrinsic or extrinsic cancer specific metabolism could module cellular malignancy in various cancers implying a possibility to develop anti-cancer schemes by targeting cancer metabolism. Multifaceted phenotypic and molecular analysis was performed to examine the changes of cellular malignancy of HNSCC cells in response to metabolic alterations, both in vitro and in vivo.

**Results:** We successfully demonstrated that external challenge (e.g. diabetic environment) as well as intrinsic metabolic gene manipulations (e.g. alteration of glycolytic and lipogenic enzymes) led to changes of cell growth, cellular motility, cell differentiation, stemness and sensitivity to chemotherapeutic agents and photodynamic therapy (PDT) in HNSCC cells via the regulations of nutrient-sensing Akt/AMPK-mTORC1 pathway. Interestingly, manipulation of individual metabolic pathway in HNSCC cells could potentially induce a gross metabolic reprogramming by targeting other metabolic cues suggesting a "cross-talks" between different metabolic machinery. Moreover, in vivo analysis demonstrated that hyperglycemic physiology facilitated chemical induced tongue tumor progression whereas expression of glycolytic/lipogenic/OxPhos enzymes regulates xenografic tumor growth. In clinic, diabetic pathophysiology positively correlated with worsen prognosis further implying the significance of imbalanced metabolism in controlling HNSCC malignancy.

**Conclusion:** Taken together, our findings indicated that external and intrinsic metabolic modulations controls cellular malignancy and therapeutic responses of HNSCC cells and could be of great potential for development of better metabolism based anti-cancer strategies in treating HNSCCs.

# Potential mechanisms of drug resistance of OSCC to cisplatin

## 口腔癌對順鉑產生抗藥性的可能機轉

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Oral squamous cell carcinoma (OSCC) accounts for almost two-thirds of head and neck squamous cell carcinoma (HNSCC) in the male population of our country. Despite the recent advancement of treatment modalities, the overall survival for OSCC remains unsatisfactory for the past decades. The therapeutic failure mainly comes from poor loco-regional control and the development of distant metastasis. Cisplatin-based chemotherapeutic regimen provides a significant survival benefit for HNSCC patients in post-op adjuvant concurrent chemoradiotherapy (CCRT) and disease control for advanced relapse diseases. However, this approach is greatly limited if tumors develop either endogenous or acquired chemoresistance to cisplatin. For HNSCC, upregulated EGFR related signaling is one of the most important pathways in the cancer formation and disease progression.. We found upon cisplatin treatment, HNSCC cell would upregulated the critical mediator of mTORC1, p62, in EGFR dependent manner to enhance its activity. The upregulated mTOR activity not only maintained the cell proliferation capacity under cisplatin treatment but enhanced properties and expanded the subpopulation of cancer stem cells (CSC) of OSCC. The CSC populations were notorious for their intrinsic resistance to conventional chemoradio therapies. When cisplatin–resistant subclones generated by gradual and long-term escalating doses of cisplatin, mTOR activity and its activator p62 were up-regulated. However, the sensitivity to cisplatin of these resistant cells was resumed by p62 knock-down or rapamycin and metformin treatment. In a cohort of advanced HNSCC patients, higher mTOR activity correlated with a poor prognosis in OSCC patients, which can be attributed to a higher local recurrence rate even after received post-operative cisplatin-base adjuvant therapy. We also found when treated with cisplatin, OSCC cells would automatically increased HB-EGF expression in a Akt/COX2 dependent manner. This signaling axis constituting a self-augmented feed forward loop was able to increase the expression of DNA repaired protein, ERCC1. This pathway may contribute to cisplatin-resistance in HNSCC patients. For the data we have, EGFR related signals play a critical role in the resistance to cisplatin-based regimes. Therefore, the combinational use of anti-EGFR drugs, like cetuximab or the under-developing Raplogs are good alternatives to overcome the induced cisplatin resistance in HNSCC. To explore other potential mechanisms may greatly benefit HNSCC patients in preventing tumor recurrence and ultimately improve the treatment outcome.

# Boron neutron capture therapy: A new treatment option for recurrent head and neck cancer

## 復發頭頸癌疾病的最新治療選擇：硼中子捕獲治療

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In Taiwan, head and neck cancer is the fourth leading cause of deaths due to cancer. More than half of the patients with head and neck cancer experienced disease recurrence, even after radical surgery, adjuvant radiotherapy, and chemotherapy. Prognosis for these patients remains dismal because there is no effective management for this intractable disease. Therefore, most of these patients die after disease relapse. There is a need for new and effective salvage management in such cases.

Boron neutron capture therapy (BNCT) is an emerging cancer treatment, although the concept was established more than 80 years ago. The efficacy of this therapy lies in its high tumor cell-killing effect with less toxicity to the surrounding normal tissue. This magical idea was first reported in 1935 by H. J. Taylor who discovered nuclear fission occurring after the absorption of thermal neutrons by boron-10 resulting in two high biologically effective particles, the "α-particle" (4He) and the recoiling lithium (7Li). These two particles can not only destroy the DNA structure of cancer cells effectively and powerfully, but also do not cause severe toxicities to adjacent normal tissues and cells due to very short emission ranges (within 5-10 μm, do not exceed the diameter of a single cancer cell of 10-20 μm). Therefore, if we can deliver boron-10 containing drugs specifically into cancer cells only and then irradiate them with thermal neutrons, we can destroy these cancer cells efficiently.

Although the concept provides a lot of promise in overcoming cancer, it still has some limitations. Two of the most important limitations are as follows: 1). Design of tumor-specific boron-10 containing drugs, and 2). Reliable provider of thermal neutron radiation. Over the past few decades, these two major problems were being solved gradually. Currently, several specific tumor-targeted boron-10 containing drugs, like BPA and BSH, have been developed after their pharmacokinetics was clearly elucidated. Traditionally, thermal neutrons were provided by nuclear reactors for BNCT research. Reactor-based BNCT has been proven effective in treating several cancers, including recurrent head and neck cancers. Most of the head and neck tumors are relatively superficial and, hence, can be irradiated with sufficient homogenous neutron flux from nuclear reactors. The outcomes were promising indeed. Recently, accelerator-based neutron sources have been under rapid construction by several heavy-industry companies globally. These accelerators can supply high-quality thermal neutron and replace the traditional reactors as a standard hospital-based treatment facility. These important breakthroughs can help in accelerating the clinical use of BNCT in the future.

# The role and mechanism of drug resistance of cetuximab in the treatment of oral cancers

# Cetuximab 在口腔癌治療之角色和抗藥機轉

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Advanced oral cancer is a highly invasive disease associated with extensive destruction of local-regional tissues and a dismal prognosis. However, management strategies for these patients are limited. In recent years, the humanized anti-EGFR antibody cetuximab is a major treatment for locally advanced or recurrent/metastatic oral cancer. In locally advanced disease, cetuximab has been demonstrated for its efficacy when combining with radiotherapy. In recurrent/metastatic disease, combination of cetuximab with standard cisplatin/5-FU chemotherapy improves the patient outcome. Regarding the mechanism of cetuximab resistance, RAS mutation has been considered as a major cause of de novo resistance to cetuximab in colon cancer patients. However, the incidence of RAS mutation is relatively rare in oral cancer patients, and the mechanism mediating acquired resistance to cetuximab in oral cancer is unclear. In this presentation, we will firstly present the result of a phase II trial which evaluates the effectiveness of incorporating cetuximab into both induction chemotherapy and chemoradiotherapy in inoperable oral cancer patients from Taipei Veterans General Hospital. A total of 43 patients were enrolled in this study. The overall response rate of induction therapy was 88.4%. One-year progression-free survival and overall survival were 43% and 68%, respectively. The result suggests that combination of cetuximab with TPF chemotherapy as an induction chemotherapy is an effective and tolerable regimen for inoperable oral cancer patients. In addition, we will also present the result of a study which demonstrates the mechanism of acquired resistance to cetuximab in oral cancer.

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## 攝護腺癌診斷與治療之新進展

# Update on the Diagnosis and Treatment of Prostate Cancer

時 間：106年6月10日 13:25~17:30

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Place：Conference Room 101A
Taipei International Convention Center

# 攝護腺癌診斷與治療之新進展

# Update on the Diagnosis and Treatment of Prostate Cancer

# Current status of mpMRI and MRI-fusion targeted biopsy for diagnosis of prostate cancer and TPE-VGH experience

# 多參數磁振造影及靶向切片診斷攝護腺癌之現況

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Systemic biopsy of prostate gland under transrectal ultrasound (TRUS) guidance in patients with elevated serum prostate specific antigen (PSA) has long been the standard practice for diagnosis of prostate cancer. However, this approach is imperfect due to low specificity of PSA and low sensitivity of TRUS biopsy in diagnosis of clinically significant prostate cancer.

In recent years, magnetic resonance imaging (MRI) has been accepted as a tool for assessment of patients at risk of prostate cancer. Multiparametric MRI (mpMRI) combines information of T2-weighted images, diffusion weighted images, and dynamic contrast enhanced MRI, demonstrates improved diagnostic accuracy of prostate cancer in terms of detection and localization of clinically significant prostate cancer. Prostate Imaging – Reporting and Data System, 2015 version 2 (PI-RADS v2) has been adopted to standardize the terminology in detection, localization, characterization, and risk stratification in patients with suspected prostate cancer who received MRI examination.

Along with the implementation of MRI in the diagnostic work-up of prostate cancer, there is growing demand for targeted prostate biopsy to confirm the nature of lesion detected by MRI. Currently available technique for targeted prostate biopsy includes MRI-guided biopsy and MRI-fusion TRUS-guided biopsy. MRI-fusion TRUS-guided biopsy is an alternative to MRI-guided biopsy, utilizing tracking device with real-time reformation of MR images during real-time TRUS scanning. This technique enabled co-registration of previously acquired MR images and real-time TRUS images, which facilitate targeted prostate biopsy.

In our institution, MRI has been performed in patients with elevated serum PSA, followed by MRI-fusion TRUS-guided biopsy for lesions with PI-RADS score $\geqq$ 3 (3 to 5). Our experiences showed the incidence of all cancer / clinically significant cancer (Gleason score $\geqq$ 7) in the lesion designated PI-RADS 3, 4, 5 were 26.7% / 6.7%, 48.9% / 34.2%, 87.9% / 48.5% ($p<0.0001$). The percentage of positive cores in the targeted biopsy specimen from lesions of PI-RADS 3, 4, 5 were 70.8%, 76.1%, 90.5% ($p=0.066$). The percentage of tumor in the positive biopsy core of lesions with PI-RADS 3, 4, 5 were 35.6%, 38.0%, 69.1% ($p<0.001$). Prostate lesion detected by MRI with higher PI-RADS score indicates a greater chance of cancer / clinically significant cancer and higher proportion of tumor in the cancer-positive cores. In conclusion, mpMRI with MRI-fusion TRUS-guided biopsy is a promising method for diagnosis of prostate cancer.

# Active surveillance for prostate cancer : NTUH experience

# 攝護腺癌的積極監控：臺大醫院經驗

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While advanced or metastatic prostate cancer may lead to mortality, men with localized disease usually have a long cancer-specific survival. Traditionally, subjects with localized prostate cancer are offered a few treatment options, including radical prostatectomy, definitive radiotherapy with or without pelvic nodal irradiation, energy ablation in select patients, primary androgen deprivation therapy (ADT) for locally advanced, symptomatic patients and those unfit for definitive therapy, and active surveillance/watchful waiting.

Active surveillance (AS) is a viable option for men with organ-confined, low risk disease (or select medium risk). It does not involve any forms of anti-cancer treatment, but is still with a curative intent by initiating definitive treatment once disease progression is detected by repeat biopsy. Watchful waiting (WW) or observation is for patients with a short life expectancy due to old age and/or co-morbidities. ADT and/or local palliative treatments will be administered when metastasis or symptoms occur.

We began to proactively counsel patients with the options of AS or WW since June 2012. A total of 142 subjects with localized prostate cancer diagnosed between December 2007 and February 2016 (follow-up for at least 12 months) were retrospectively enrolled for the study. After excluding 15 patients with misclassification or loss to follow after the first visit, 127 men remained in the study. Data were updated until March 2017. Routine eligibility criteria depends on life expectancy and include < clinical T2b, low Gleason score (<3+4=7), low positive cores (33% of cores biopsied), low percentage of cancer in positive cores (< 50%), and low PSA (<10-15 ng/ml). However, criteria vary according to physician's judgement on life expectancy, co-morbidities, and cancer phenotype.

The median age at diagnosis of the 127 patients was 68.3 years. Median follow-up was 27.9 months. The median PSA at diagnosis was 7.7 (mean 10.0) ng/ml. Clinical T1, T2, and T3 disease were seen in 75%, 24% and 1% of patients, respectively. According to D'Amico classification, 41%, 44%, 12%, and 3% of patients belong to low, medium, high, and unclassified risk groups, respectively. The percentage of subjects with Gleason score <=6, 3+4, 4+3, and >=8 was 69%, 22%, 6%, 3%, respectively.

Among the 127 subjects, 42 (33%) never did a rebiopsy (confirmatory biopsy) to ensure the feasibility of AS. Fifty-seven (45%) patients underwent a confirmatory biopsy within one year of diagnosis at a mean of 4.8 months after the first diagnosis. Among them, 53, 19, and 3 patients underwent 1, 2, and 3 rebiopsies (excluding the confirmatory biopsy), respectively during the course of AS. The median interval between each re-biopsy was 20, 20, and 17 months, respectively. Overall, 22 (17%) of the 127 subjects showed histological progression after re-biopsy. During the confirmatory biopsy, 8 (14%) patients had a pathology progression that prompted the suggestion of definitive treatments. Interestingly, among 20, 27, and 10

subjects with low, medium, and high risk disease, 3 (15%), 5 (19%), 0 (0%) subjects, respectively showed a pathology progression and 11 (55%), 3 (11%), and 3 (30%) patients, respectively showed no malignancy at all upon the confirmatory biopsy.

Among the 127 subjects, 104 (82%) men were still kept on AS during the followup period. A total of 23 men (18%) shifted to undergo definitive treatments, including 5 patients with robotic radical prostatectomy and 18 patients with external beam radiotherapy. There was no death in our cohort yet.

AS appears to be a viable treatment option for Taiwanese patients with localized prostate cancer, if patients are selected properly. Longer follow-up is needed to confirm its clinical role in the management of localized prostate cancer patients.

# Prophylactic robotic-assisted laparoscopic radical prostatectomy for preoperatively suspicious prostate cancer: Clinical outcomes of 125 cases

# 術前疑似攝護腺癌患者的達文西機器手臂輔助腹腔鏡預防性攝護腺根除術：125 例的經驗

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**Background:** Novel indication are reported for patients with preoperatively suspicious prostate cancer received Prophylactic robotic-assisted laparoscopic radical prostatectomy (P-RARP) performed by experienced surgeons. To report clinical outcomes with 125 cases of P-RARP for preoperatively suspicious prostate cancer.

**Methods:** This retrospective study reviewed data of a subset of 125 consecutive patients who underwent P-RARP in 114 cases and Prophylactic laparoscopic radical prostatectomy(P-LRP) in 11 cases for preoperatively suspicious prostate cancer performed by two surgeons Pathologic characteristics and outcomes of patients with suspected prostate cancer were analyzed and preoperative, intraoperative and postoperative parameters were compared between three groups. Patients were stratified by final pathology reports of RARP specimens: Group I: Prostate cancer, N=53(42.4%); Group II: Abnormal (PIN: prostate intraepithelial neoplasia; ASAP: atypical small acinar proliferation ), N=39(31.2%); Group III: Benign (NH: nodular hyperplasia or inflammation), N=33(26.4%).

**Results:** Mean preoperative prostate specific antigen (PSA) was 17.04±2.31ng/mL. Intraoperative parameters included console time 116.7±3.24 min, blood loss 92.1±9.02 ml and mean prostate volume 64.41±3.33 $cm^3$. No patients required blood transfusions. Two grade I complications (Clavien system) were noted. Statistically significant improvements were found in uroflow rate, post-voiding residual urine and symptom scores (all $p<0.0001$). World health organization (WHO) Quality life score was significantly improved from 3.82 to 0.33). Postoperatively, urinary continence was achieved 98.4%. Potency rate at one year in was 88.9%.

**Conclusion:** Prophylactic RARP with bilateral neurovascular bundle preservation have excellent function outcome for preoperatively suspicious prostate cancer performed by experienced surgeons.

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## 發炎性腸道疾病的跨科整合與治療新趨勢

# Inflammatory Bowel Disease: Multidisciplinary Approach and Trend

時 間：106年6月10日 13:30~17:30

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Taipei International Convention Center

# 發炎性腸道疾病的跨科整合與治療新趨勢

# Inflammatory Bowel Disease: Multidisciplinary Approach and Trend

# The differences of IBD between eastern and western, experience from Taiwan

## 從台灣出發，看發炎性腸道疾病東西方的差異

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Inflammatory bowel diseases (IBDs), used to be presumed as the Western disease, since their prevalence and incidence increased significantly after the 1950's in Western countries. This phenomenon spread to Asia, including Taiwan, after the 1980's. Although the significantly increased of both the ulcerative colitis (UC) and Crohn's disease (CD) in Taiwan, the incidence and prevalence was still lower than the reports from the Western countries. The gender ratio for IBDs is almost equal in the Western, but in Asia, male is still more prevalent for IBD, though female is catching up recently.

The pathogenesis of IBDs are thought to be related to the genetic, environmental, and immune factors. With the progress in the genetic analysis, we understood that the genetic background is different between the Eastern and Western. The concordance rate of twins, the family history with IBDs are lower in the Eastern than the Western. While NOD2 (CARD15), IRGM, IL23R play major roles for the Western's CD, TNFSF15 is the only CD associated gene validated in Korean, Japanese, Chinese, and Taiwanese.

Thiopurine is a commonly used immunomodulator for IBD patients. In Western countries, the standard dose is 2-2.5mg/kg/d. However, when we use this dosage, more than expected number of patients suffered from leukopenia was observed in Asia. NUDT15, found by Korean's genome wide associated study, was confirmed to be the possible genetic background to explain this difference.

Local endemic diseases, for example, the hepatitis B and tuberculosis, also affect the management of IBDs. Compared to the practice in Western, we need to exclude and monitor more cautiously about tuberculosis in Asia.

Although there are differences about IBDs in Western and Eastern, the effort we putting in disease awareness and improvement in quality of care are the same.

# The biologic treatment in ulcerative colitis: Current evidence

## 生物製劑在潰瘍性結腸炎的角色

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Ulcerative colitis (UC) is a major form of inflammatory bowel disease (IBD), characterized by chronic inflammation involving the colon and rectum. It is a cause of significant morbidity worldwide and its incidence and prevalence appear to be increasing with time. Patients with UC frequently experience episodes of bloody diarrhea with or without mucous, abdominal pain, fever and weight loss. For most people, ulcerative colitis has a frustrating pattern of flares and remissions. Therefore, two main goals of treatment for ulcerative colitis are to reduce symptoms (achieve remission) and prevent symptoms flare (maintain remission). Among the pro-inflammatory cytokines, the role of TNF-α has been the most extensively studied. Excessive production of TNF-α from activated macrophages and T-lymphocytes leads to further activation of macrophages and T-lymphocytes, expression of adhesion molecules on vascular endothelium and recruitment of neutrophils, resulting in a vicious cycle of increasing inflammation. TNF-α is expressed at high levels in the colonic mucosa of patients with UC and has been considered to play a central role in the pathogenesis of UC. Anti- TNF- α biologics have profoundly influenced the management of UC patients, especially those with refractory disease. Dr Sung-Ae Jung is the professor of School of Medicine at Ewha Womans University Hospital and has extensive clinical experience of treating IBD. She is the main principle investigator of the multicenter registry of IBD led by Korean Association for the Study of Intestinal Disease. In this lecture, she will talk about the role of anti-TNF-α inhibitors in ulcerative colitis in achieving mucosal healing and symptom relief. She will share the registry data from South Korea and how anti-TNF-α inhibitors performed in the real-world setting in terms of efficacy and safety.

# The role of radiologist in management of IBD patients

## 放射科醫師在發炎性腸道疾病治療的角色

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The incidence of Inflammatory bowel disease (IBD) is increasing throughout the world, including Asia. Conventional endoscopy with biopsy is the reference standard for assessing mucosal disease activity of IBD. However, it is invasive and gives limited information about transmural and extraenteric disease extent. Over the years, multiple imaging modalities have been used to investigate the small bowel and colon. Unlike an enteroclysis technique that requires intestinal intubation, MR and CT enterography with oral administration of neutral contrast agents developed as a noninvasive alternative for bowel loops evaluation are becoming increasingly used .

This presentation will review the MR and CT enterography technique and provide practical tips in imaging interpretation.

# Surgical management for IBD patients: When and how

## 外科手術在發炎性腸道疾病治療的角色

**Kazuhiro Watanabe**

*Department of Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan*

Surgery for inflammatory bowel disease (IBD) has become safer and less invasive and has been refined to offer a better quality of life to IBD patients.

In terms of Crohn's disease (CD), it is estimated that up to 80 % of patients with CD will require at least one intestinal surgery during their course. The rates of surgical recurrence from the first surgery are reported to range 16- 36 % at 5 years and from 28-55 % at 10 years. Then, CD patients often require multiple surgeries, which increases the risk for intestinal failure (IF). The cumulative risk of IF after the initial surgery was 0.8 % (5 years), 3.6 % (10 years), 6.1 % (15 years), and 8.5 % (20 years) in Japanese multicenter study (Watanabe K, et al. J Gastroenterol. 2014). There are some surgical techniques for CD to avoid the occurrence of IF. Strictureplasty is a well-established surgical procedure for fibrostenotic obstructive disease, which widen the luminal diameter without bowel resection. In terms of anastomotic technique, functional end-to-end anastomosis is one of the most standard techniques. We recently performed "antimesenteric cutback end-to-side isoperistaltic anastomosis" (Tohoku University's method), as a new reconstructive procedure.

In terms of ulcerative colitis (UC), the standard procedure is a 2- or 3-staged restorative proctocolectomy with an ileal pouch-anal anastomosis (IPAA). With advances of laparoscopic devices and experience of laparoscopic surgery, several studies have reported the feasibility and safety of laparoscopic surgery for UC in the elective setting. Though laparoscopic surgery was also induced in patients with severe UC, standard laparoscopic surgery for severe UC is still technically difficult because of bowel friability and hypervascularity, creating a high likelihood of perforation and bleeding. In the acute setting, hand-assisted laparoscopic surgery (HALS) is a useful surgical technique in which laparoscopic procedures are performed with the aid of a hand inserted into the abdomen through a small incision. Surgeons are enabled to obtain tactile sensation, manual retraction, and digital vascular control, which could allow complex laparoscopic operations to be performed more effectively and satisfactorily (Watanabe K, et al. Dis Colon Recum. 2009).

# Role of the pathologist in the diagnosis and management of IBD

## 病理科醫師在發炎性腸道疾病診斷與治療的角色

**Wen-Yih Liang**

梁文議

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Inflammatory bowel disease (IBD) is rare in Asia in the past. Today, the importance of IBD in Asia is exemplified by its rapidly increasing incidence, complicated disease behavior, and substantial morbidity. (From 0.60 to 3.44 per 100 000)

Diagnosis and classification of IBD depend on a combination of clinical, endoscopic and pathological features. Several entities can mimic IBD clinically and histologically. Correlation of histological features with clinical and endoscopic findings is essential and is facilitated by participation in multidisciplinary meetings where IBD cases are discussed. Indeed, better interaction between histopathologists and endoscopists has been formally recommended in clinical guidelines.

The reasons for taking a biopsy include: confirmation of the diagnosis of IBD, distinction between UC and CD, exclusion of dysplasia, exclusion of coexistent conditions or complications and the activity and extent may also be assessed.

Histological evaluation of endoscopic biopsy samples and resection specimens is an important component of the diagnosis and management of patients with IBD. Unfortunately, many problems inherent to IBD pathology remain the subject of intense scrutiny and debate. These problems include, but are not limited to, lack of standardized and/or validated diagnostic criteria, lack of uniformity in diagnostic reporting, lack of specificity of histopathological features, lack of adequate clinical correlation.

In summary, a detailed clinical information, adequate sampling and good communication between physicians and pathologists can make great improvement in the diagnosis and treatment of IBD.

# Perioperative management of inflammatory bowel disease

## 如何改善發炎性腸道疾病手術前後的治療與追蹤

**Peter R Gibson**

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Major surgery is common (up to 70%) in patients with Crohn's disease and is needed in 20% of patients with ulcerative colitis, despite considerable advances in the therapeutics. Short-term outcomes from surgery are influenced by pre-operative optimisation and disease recurrence can be impacted by post-operative management strategies in patients with Crohn's disease. The timing of surgery is an important predictor of outcome. In acute severe ulcerative colitis, delaying surgery beyond the time when futility of medical management is reached or when features of impending perforation are present increases post-operative morbidity and mortality. In Crohn's disease, there is a balance between aggressive medical therapy attempting to get the patient in premium condition for surgery (draining abscesses, using antibiotics and reducing inflammation) and the effects of prolonged exposure to drugs that might impair healing or increase the risk of infection; this balance has to be individualised utilising clinical experience and acumen of a multidisciplinary team. However, there are several aspects that need attention in nearly all patients facing surgery. These especially include psychological and nutritional management, the cessation of smoking, prophylaxis against thromboembolism (essential in all patients), and minimisation of therapies that do impact on post-operative course, such as high-dose corticosteroids. Nutritional repletion of the undernourished patient is clearly of importance. This applies equally to macronutrients and micronutrients; for example, healing ability should optimised by, for example, protein and zinc repletion, and the ability to cope with operative blood loss will be improved by attention to anaemia per se and to iron repletion. The use of pre-operative exclusive enteral nutrition has benefits in patients with Crohn's disease due to its ability to replenish nutrition and to reduce inflammation.

A strategy of medical management of Crohn's disease post-curative resection is essential in order to reduce the risk and severity, and to mitigate the likelihood of repeated surgical resection. Randomised controlled trials have provided quality guidance on a stratified approach to drug therapy together with surveillance techniques (faecal calprotectin, colonoscopy) to pick up recurrence early requiring escalation of therapy. For ulcerative colitis, the issues are quite different and relate more to the timing of second and third-stage procedures following colectomy. Nutritional issues in this setting are less prominent as the patients are generally well. However, psychological issues and education about outcomes become key aspects requiring active intervention.

Hence, optimal perioperative management of patients with IBD is a multi-disciplinary responsibility that includes the gastroenterologist, surgeon, IBD nurse, psychologist, dietitian, pharmacist and, most importantly, patient.

# 12

## 虛擬實境與模擬醫學國際新趨勢

# Trends of Augmented Reality, Virtual Reality and Medical Simulation

主辦單位：臺北榮民總醫院教學部

時 間：106年6月10日 12:30~17:30
Time：June 10, 2017 12:30~17:30

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

# 虛擬實境與模擬醫學國際新趨勢

# Trends of Augmented Reality, Virtual Reality and Medical Simulation

# Trends of augmented reality, virtual reality and medical simulation

# 虛擬實境與模擬醫學國際新趨勢

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**Opening Remarks**

Established in 2003, the Center of Clinical Skills Training marks our pioneering role in the country for Interprofessional high-fidelity medical simulation training. In 2011, the Interprofessional virtual reality teachers training model was first established in Asia. In 2013, the series of interprofessional high-fidelity medical simulation books and DVDs were published nationally after continuous integration of the whole faculties. The published high-fidelity medical simulation materials were sold to the 17 clinical skills centers in teaching hospitals at the northern, central, and southern of Taiwan, and the promotion probability was nearly 80%. In 2015, the first construction of interprofessional, multi-disciplinary medical simulation courses with the SimMan ® 3G, SimMon and SimNewbaby were established. Since 2015, the interprofessional teams had won gold, silver, bronze medal and potential awards many times in the High Fidelity Simulation of Healthcare Quality Improvement Campaign (HQIC) by the Joint Commision of Taiwan. The innovative training models of high-performance virtual-reality and medical simulation had attracted domestic and foreign medical education groups and students to frequent visits. The unique innovative training models in high-performance virtual-reality and medical simulation had gotten the high satisfaction in trainees, too. In recent years, the medical education SCI articles were also published continuously.

**開幕致詞**

本院於民國 92 年起，領先全國於臨床技能中心，建置跨領域醫學模擬演練區。並於民國 100 年，建置領先全亞的跨領域虛擬實境教師培育訓練之模式。並於民國 102 年起，持續整合全院師資，領先全國出版系列跨領域高擬眞醫學模擬書籍及光碟；本院出版之高擬眞醫學模擬多媒體教材，分別行銷至全國北、中、南 17 家具臨床技能中心的教學醫學，其推廣涵概率近 80%。本院並於 104 年首波建置以 SimMan® 3G, SimMon 及 SimNewbaby 高階醫學模擬人為主，建置跨領域多專科醫學模擬帶狀課程。自民國 104 年起，本院籌組的跨領域團隊，在醫策會主辦的高擬真競賽中，也多次榮獲金、銀、銅牌、及潛力獎。本院建置之高效能虛擬實境及醫學模擬創新訓練模式，吸引國內、外醫學教育團體及學員來頻繁參訪。本院獨有的高效能虛擬實境及醫學模擬創新訓練模式受訓學員之滿意度高。近年持續有醫學教育 SCI 文章的發表。


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# Application of virtual reality classroom in clinical teaching

# 虛擬實境教室於臨床教學的應用

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Nowadays, virtual reality (VR) is broadly applied in entertainment. However, the experience of applying it in education, especially in clinical education, is few. Taipei Veterans General Hospital built an innovative classroom and designed training module for faculty development in 2011. Here we share our experience of how we trained faculty to apply virtual reality classroom in clinical teaching. The virtual reality classroom was equipped with six projectors and an annular screen to project six video clips, which created five simulated situations of clinical teaching, including bedside teaching, outpatient clinic teaching, lecture-based teaching, operatory room teaching, and emergency room teaching. Also, we created many teaching case scenarios to simulate the real teaching situation.

To apply the virtual reality classroom in clinical teaching, we invited simulated patient and simulated student to prompt out some difficult situations in each case scenario, such as student with low learning motivation or patients with unreasonable demands. In the training, we also invited a senior faculty to be the facilitator in the small group discussion. The facilitator was to facilitate the whole process, give feedback to the attendants and guide the small group discussion. Through the enhancement of virtual reality classroom, we designed a successful module for faculty of medical professionals.

Modern technology makes life more convenient and better; meanwhile, new technology makes faculty training more effective and easier. This is an innovative and creative training module in Asia, and people from different countries are amazed by the design. We share our experience of applying VR in faculty training module and hope you enjoy it.

# The training and application of standardized patients

# 標準化病人的訓練與應用

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Holistic medicine has become the mainstream of today's medicine. Learner-centered approach is increasingly important in medical education.

"Standardized Patient" (SP) provides an extremely valuable resource to combine holistic medicine and Student-centred learning, creates a cross area model of training and examination, help future doctors develop and evaluate clinical skills through the imitation in drama.

This presentation will explore the different ways of performance training to SP and real actors from the perspective of a dramatic worker. Using the Drama theory includes creative drama, story theater and the method of Stanley Slavsky to improve immersion, case development and how to train SPs. Make the module of performance skills in different grades to keep consistency of standard clinical simulation of individual standardized patient should be strictly enforced and assured.

Looking forward to promote cooperation between Art and Medical science, hope our experience will help to establish a distinct SP training program specifically adapted to Taiwan.

全人醫療是現今醫學主流，以學習者為中心的醫學教育日漸重要。標準化病人 (standardized patient) 結合全人醫療與學習者導向兩大核心精神，透過戲劇領域的模倣扮演，訓練醫學生臨床技能，是一種跨領域的學習與測驗模式。

本次從戲劇工作者的角度，探討標準化病人與真實演員在表演訓練方法上的差異。透過創作性戲劇、故事劇場、史坦尼斯拉夫斯基表演方法等戲劇教學理論，落實於標準化病人的表演能力、教案撰寫及整體培訓。

同時提出階段化的表演整合模組，加強標準化病人在表演上的擬真及一致性。展望藝術與醫學兩門學科相互合作，締造更適合台灣的標準化病人訓練形式。

# The application of Entrustable Professional Activity (EPA) in standardized patients

# 應用 EPA 於標準化病人訓練

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Standardized patients (SP) mean people, who receiving proper training, can simulate clinical cases. The reliability of Objective Structured Clinical Examination (OSCE) was effected by the factors include the raters, the number of stations, scoring checklist, standardized patients, and the interaction of these factors. The report of Lubna A Baig et al in 2014 noted that, in OSCE, the same case of different track and at different times, standardized patients presented variability, which would result in a significant error of the assessment. The values of Cronbach's alpha were between 0.40-0.74.

Milestones and Entrustable Professional Activities (EPA) are competency-based training and assessment models, which are new changes in the United States and Canada for graduate medical education training programs in recent years. In the standardized patients' training, we can also use the concept of milestones and EPA to design the training program, so that standardized patients know the training targets to achieve the milestones and EPA. Raters, SP trainers or teachers can assess the performance of SPs according to the milestones and EPA.

The goals and objectives are as below:

First, we would set the milestones and EPA in the standardization patients' training program.

Second, we would apply the milestones and EPA in standardized patients training and as an evaluation of the portrayal of standardized patient.

Third, we would investigate the effectiveness and impaction of standardized patients' training by milestones and EPA.

Fourth, we would investigate the views of standardized patients, SP trainers, instructors and raters in the OSCE of standardized patients' training models.

# Compassionate conversations: Learning to deliver difficult news through standardized patient exercises

## 慈悲的對話：透過標準化病人學習如何告知困難消息

**Susan Eller**

*Immersive and Simulation-based Learning, Stanford School of Medicine, C.A. USA*

**Introduction:**

Effective communication skills are essential in providing safe, patient-centered care. Communication is both the most common procedure involved in healthcare and one of the most frequent causes of errors. In addition to optimizing patient safety, a clinician needs to be able to deliver difficult news to patients and family members. Types of difficult news can range from disclosure of errors, to bad test results, and even death notification. If done poorly, this type of communication can have a devastating effect on patients and family members, making a bad situation even worse. This type of communication skill is not consistently taught in professional educational programs; however simulation-based learning strategies can improve practitioner's skills.

This presentation discusses techniques for training healthcare professionals thorough and compassionate methods for delivering difficult news through communication exercises with standardized patients (SP), and feedback from faculty and the SP.

**Content and structure:**

The presentation will start with a brief scenario of a patient (SP) who has a terminal diagnosis and the healthcare team needs to have a discussion regarding the patient's wishes for care. A short debriefing of the participants will then be followed by an explanation of how the scenario was constructed and what training is necessary for the SPs to provide summative or formative exercises. The discussion will conclude with a review of recent trends in the literature and at Stanford for SP communication exercises.

**Anticipated outcomes:**

By the end of the presentation, the participants will:

- Discuss the use of SPs for training healthcare providers to deliver difficult news.
- Describe training protocols for the SP.
- Analyze the risks and benefits of using checklists for SP communication exercises.

**Allotted time:**

60 minutes

# Trends of medical simulation, augmented reality and virtual reality

# 模擬醫學與虛擬實境國際新趨勢

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To ensure patient safety, the team collaborative involvement of health professional is necessary to delivery patients' care with chronic medical/mental health conditions and social disadvantage. Inter-professional practice collaboration (IPP) is a model of healthcare which optimizes the use of multiple professional skills sets to provide well-coordinated, high-quality and patient-centered care. Inter-professional education (IPE) is a way of improving patient-centered and team-based care through positive shared learning activities in a non-threatening environment to respond to patient′s needs. IPE aims to improve the coordination, communication, teamwork, leadership skills of health professionals.

Simulation-based IPE offers an effective platform for IPP, providing different health professionals with valuable learning experiences through communication. This lecture focuses on discussion of effectiveness of the integration of TRM into the simulation-based IPE in the trainee's proficiency of IPP in clinical wards.

Like IPP, Team resource management (TRM) includes core elements of communication, leadership, mutual support and situation monitoring. In other words, the core elements of IPP and TRM are overlapped excluding mutual support and situation monitoring. In addition to IPE, for establishment of IPP competency, TRM 7-step debriefing checklist is an ideal tool to augment TRM proficiency. The seven steps TRM-debriefing checklist including clearly communication, understanding each other role and responsibility, keep alert and handle critical situation, reasonable workloads, ask and provide help, avoid/induce mistake, the points that need improvement. The ISBAR strategy including Introduction, situation background, assessment, recommendation; STEP strategy including status of patient, team members, environment, progress forward goal. In order to ensure the safety of patient, the health professionals should familiar with both IPP and TRM. Preliminary, our team merges IPP+TRM in our simulation-based training. By the clinical scenario developed by young health professionals, this IPE+IPP+TRM(IIT)-mixed model training is undergone through description-analysis-application (DAA)+TRM 7-step debriefing checklist protocols to stimulate their holistic patient care abilities. Within the post-2-years, we had completed 12 inter-professional Clinical scenarios, that incorporating in the regular IPE sessions. Continuously, the IIT clinical scenario videos are produced to share this new model with others.

# The standardized patient's views of the holistic medical care-based clinical skills training

## 標準化病人眼中的『全人醫療教育臨床技能訓練』

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Standardized patients are widely used for teaching and assessment. In a national survey of clinical communication assessment in medical education in the United Kingdom, the Objective Structured Clinical Exam (OSCE) was the most commonly used method of assessment. All medical schools in the United States, Canada, Korea, and Taiwan now include a nationally standardized assessment of clinical history taking, physical examination skills, and patient-doctor communication skills, as part of the qualifying examinations.

Holistic medicine is a form of healing that considers the whole person – body, mind, spirit, and emotions – in the quest for optimal health and wellness. According to the holistic medicine philosophy, one can achieve optimal health – the primary goal of holistic medicine practice – by gaining proper balance in life. For medical students, the holistic medical care-based clinical skills training are to build up holistic doctors of the future. Standardized patients play important a vital role in the holistic medical care-based clinical skills training. We aim to understand the views of the holistic medical care-based clinical skills training from the perspective of standardized patients.

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## 大數據與生物資料庫研討會

# Big Data and Biobank in Taiwan

時 間：106年6月10日 13:30~17:30

Time：June 10, 2017 13:30~17:30

地 點：台北國際會議中心 101D 會議室

Place：Conference Room 101D
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# 大數據與生物資料庫研討會
# Big Data and Biobank in Taiwan

# Big data research and precision medicine

# 大數據研究與精準醫療

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Big data research based on real world health care data has become an important trend in these years. Precision medicine initiatives proposed by President Obama is actually an ultimate big data project. Curing either rare diseases or common cancers does not just requiring more trials, but also linking all the data the researchers or physicians already have. Nationwide population-based studies have several advantages compared with traditional cohort studies and randomized clinical trials.

In this talk, we will use our previous big data research experience based on Taiwan's National Health Insurance Research Database (NHIRD) as examples to introduce the feasibility of big data approach in precision medicine. Based on NHIRD, we found several methods to prevent digestive cancers based on patients' characteristics. We found early Helicobacter pylori eradication and regular use of non-steroidal anti-inflammatory drugs (NSAIDs) associated with reduced risk of gastric cancer. We reported that antiviral therapy was effective as a 2nd chemoprevention agent to reduce hepatocellular carcinoma (HCC) risk in patients with hepatitis B. Antiviral therapy and NSAIDs were also an effective 3rd chemopreventive method to reduce HCC recurrence in patients with HBV and HCV-related HCC after liver resection or radiofrequency ablation (RFA). In addition, we found regular ultrasonography and higher RFA operator volume significantly associated with HCC mortality.

Big data approach can also be used for personalized risk prediction and finding the molecular signaling pathways to inhibit carcinogenesis. For patients with peptic ulcer diseases, we used NHIRD to construct a nomogram to predict each individual patient's risk score and categorized patients' risk in the following 2 years. We also used NHIRD to find the usefulness of metformin and statins to treat HCC and explored the related signaling pathways with in vitro and in vivo studies. Currently, we are conducting a nationwide multicenter randomized clinical trial to confirm the chemopreventive effect of statins in HCC.

In conclusion, big data approach can be used to conduct novel clinical studies, to assess effectiveness in real world, to make health policies, and to achieve precision medicine.

# Establishment and application of big data database: Taiwan's experience

# 大數據資料庫之建置與應用：台灣經驗

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Geographic information system (GIS) layers different types of data on top of one another. The cross referencing function makes our life much more convenient by using GIS. Similarly, a bio-GIS, which integrates the genome, transcriptome, proteome, disease phenotype, life style, clinical trial information, etc. together, will be useful for biomedical research as well as for translational medicine. To integrate big data, using noSQL database to build a data warehouse is more flexible and more efficient than using the traditional relational database. Therefore, a graph database called Neo4J was used to build the data warehouse. A data mart can easily be constructed from the data warehouse. The GUID (global unique identifier) was used to integrate the de-identified data. The integrated data in the data mart can then be processed by using R, visualization software, etc.

This integrated database approach has been applied to the studies of schizophrenia and cancer. Schizophrenia is a complex disease, which has multiple risk factors. To explore the possible mechanism of this disease, we examined the synergistic gene interactions by using the gene variation data and the results of an endophenotype, i.e. the score of continuous performance test (CPT). The test score was integrated with the exome sequence data, protein-protein interaction. Those genes that may interact with each other were overlayed on a protein-protein interaction network. A disease mechanism was proposed to explain the interaction of synergistic gene interactions. By using the survival data and microarray gene expression data, it is possible to identify synergistic gene pairs, which may lead to poor survival in breast cancer patients. Taken together, integrating the phenotype and genotype data may get meaningful results by using the data mining approach.

# The establishment of biobank in Hospital: The experience of Taipei Veterans General Hospital

# 醫院生物資料庫之建置：以台北榮總為例

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A biobank aims to collect biological samples and human tissues so that researcher have access to these valuable samples in order to facilitate research and development in biological and medical sciences.

Most of the disease are not caused by a single factor. The establishment of biobank for specific diseases or populations to prevent disease is important. Comply with government regulations to establish biobank in hospital. And the ethical principle of Biobank is respecting for patients' privacy and discretion. It is expected that the established biobank will provide more contributions to the study of specific diseases or populations.

The VGHTPE Biobank is designed to improve the quality of facilities that collect, process, store, and distribute biospecimens for research. It has two -20oC freezers, twelve -80oC freezers and six large liquid nitrogen freezers. All freezers are on backup emergency power and are monitored their temperature. The VGHTPE Department of Information Management has established an electronic biobanking inventory system called STS (Sample Tracking System). It tracks sample location, freezer number, rack number, box number, and derivative products. It helps biobank staffs more efficient at work and improve the quality of storage.

To protect patient privacy, all specimens received by the bank are immediately de-identified by our biobank staffs and the linkage codes are maintained solely by the VGHTPE Biobank in the isolation room without internet connection. The request for biospecimens by a researcher must be approved by VGHTPE IRB and our Biobank Ethic Committee. These two approvements make sure the project comply with government regulations.

These resources revealed that our biobank is a standardized biobank that provides high-quality biological specimens to researchers who adopted our biobank specimens.

# Governance of large scale biobank: Taiwan biobank and its discontent

# 大型生物資料庫之監督與管理：以中研院台灣生物資料庫為例

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Although large population-based biobanks that store both biological samples and personal information for unspecified future uses provides unprecedented potential for biomedical research, it also poses major challenges to the traditional approach of project-specific consent.

Realizing that a scientific undertaking without social legitimacy and a deviation from the autonomy-based approach without social support would jeopardize the operation of biobanks, advocates have placed their attention on how to set up a governance structure that helps build public trust and to develop an alternative rationale to justify the practice of broad consent. While ethics governance committees are widely adopted as a trust building mechanism, it has long been debated whether public trust in a scientific undertaking can be obtained simply by adding an extra layer of operation oversight without engaging directly in the deliberation on social desirability and legitimacy. Alternatively, reciprocity has been separately proposed to be the moral ground for the substitution of project-specific consent in biobanking.

However, a weak and uncertified operation oversight even equipped with secured pseudonymization of samples and data would not cure the injury of autonomy loss in default of providing information about how those samples and data are actually used back to the participants. Framing the current disputes over whether newly added diseases arms and bio-signature studies conducted by the management team of the biobank itself need to be reviewed externally as a power contest between IRB and EGC also misses the point that the two mechanisms have different functions. All these discontents provide an invaluable chance to review and reform the current governance scheme of Taiwan Biobank.

# Current process of biosingnature research for type 2 diabetes in Taiwanese population

# 台灣糖尿病生物標誌研究現況

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Type 2 diabetes (T2D) is a complex disorder, leading to irreversible damage in a number of tissues, especially the retinal, kidney glomerulus, blood vessel, and nervous tissues. In order to enhance understanding of the prognosis of diabetes and create the risk calculators for different diabetic complications outcome, our research team used the genetic, proteomic/ metabolomics and epigenetic approach to identify different type of biomarkers that can be used to predict the development and progression of diabetic nephropathy (DN) and diabetic retinopathy (DR), and also to predict the response for anti-diabetic drug (dipeptidyl peptidase-4 inhibitor (DPP4i)) among Taiwanese population.

We identified genes related to T2D, DR and DPP4i drug response via whole genomic association study (GWAS) and replicated the genes reported from previous reports in our population. With more susceptibility genes were identified, the area under curve values for predicting diseases development were increasing. Furthermore, among those novel genes we identified, we found that low expression level of the protein tyrosine phosphatase receptor type delta (PTPRD) gene was observed at the onset of the disease and throughout the disease progression via hypermethylation mechanism. Using a multifaceted genomic analysis approach, we determined that PTPRD is inactivation via both genetic and epigenetic mechanisms in T2D.

DN is one of the major micro-complication of T2D. Because protein is the real functional substrates of bio-mechanisms, we conducted proteomic and metobolomic studies to discover the novel biomarkers in urine and plasma. Several protein and metabolite markers for early prediction of DN were identified and were validated in a large amount of samples. Our results showed that some urinary proteins are present while albumin level is still low. The results may imply that some of the patients have slight glomerular and tubular damage and will not be detected by traditional urinary albumin creatinine ratio method.

Biosignatures of T2D involve a combination of genetic/proteomic/epigenetic markers and clinical data. The increasing ability to accurately predict the risk of T2D and its complications and the drug response could have an impact on individual therapeutic or preventive interventions, thus reducing healthcare expense and loss of life expectancy.

# Biosignature study of Alzheimer's disease in Taiwan

# 台灣阿滋海默症生物標緻研究

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Alzheimer's disease (AD) is the most common cause of dementia and mild cognitive impairment (MCI) is a transitional stage between normal aging and dementia. The AD biosignature study aimed to decipher the potential biomarkers of AD in clinical, genetic, neuroimaging, and biochemical aspects. We have enrolled 1,158 patients (75.2% AD and 24.8% MCI) from August 2012 to March 2017 in 4 teaching hospitals. The yearly follow-up rate was 70~75%. During the follow-ups, 31.5% AD patients showed rapid MMSE score decline ( $\geqq$ 3 points per year). Among the MCI patients, 34.5 % patients converted to AD and the conversion rate was 19.7 converters per hundred patient-years.

In clinical and biochemical studies, we found that AD and MCI patients showed higher MCP-1, lower 25-hydroxy-vitamin D, and higher clusterin levels compared with controls at the base-line. Using longitudinal analyses, AD and MCI patients with high clusterin, low Aβ1-40 and Aβ1-42 had a higher chance to show rapid decline of MMSE scores during the 3-year follow-up. In contrast, high MCP-1 was associated with a rapid decline of MMSE scores during the 1-year follow-up. Besides, we also found low Aβ1-40 and Aβ1-42 might be associated with behavioral and psychiatric symptoms.

We performed genotyping of 12 AD genes (PICALM, CR1, ABCA7, CLU, MS4A6A, BIN1, CD33, SORL1, GAB2, EPHA1, and APOE). The results showed significant difference between patients and controls in APOE, ABCA7, and SORL1. ABCA 7 rs3764650 GG genotype may carry a reduced risk for AD. We also found G allele of SORL1 rs1784933 was associated with a lower risk of AD and lower plasma Aβ1-42 level. These results confirm ABCA7 and SORL1 SNPs may influence AD susceptibility in the population in Taiwan.

In neuroimaging studies, we found that the MTA (median temporal atrophy) scores showed a significant association with MMSE and CDR-SB, while the right side PA (posterior atrophy) scores were significantly associated with NPI-agitation/aggression subscales. Besides, the plasma Aβ1-42/Aβ1-40 level was correlated with MTA scores. The plasma clusterin level was correlated with right-side PA scores. The results indicated the plasma Aβ1-42/Aβ1-40 ratio and clusterin level may be associated with different clinical symptoms and regional brain atrophy. Overall, the cross-sectional and longitudinal studies showed promising biomarkers in the clinical pathway of AD.

# Taiwan biosignature study for cardiovascular disease

# 台灣心血管疾病生物標幟研究

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**Background and methods:** Cardiovascular disease (CVD) is the leading cause of death worldwide and is associated with considerable mortality and morbidity. Although great effort has been applied to modify risk factors to reduce the occurrence of CVD, rates of CVD and mortality continue to increase. Cardiovascular disease is a very complex disease which involves multiple biological pathways including lots of mediators, genes, environmental risk factors, and gene-environment interactions. In addition to traditional risk factors such as hypertension, diabetes, dyslipidemia, and smoking, biomedical researchers keep a watchful eye on any gene, protein, or metabolite expressions that could serve as biomarkers indicative of early disease phenotypes, or predictive of disease progression and outcome. The integrative computational approach with combination of biochemical markers and proteinomics data as well as different types of protein interaction data could explore the new and dimensional views of the complex underlying mechanisms of the disease.

**Results:** In our current consortium including nine medical centers in Taiwan, more than 2000 advanced CAD patients who have received coronary intervention treatment were enrolled and followed for more than one year. Although these patients are controlled well adhering to current treatment guideline, an increased baseline inflammation status still was observed in patients developing adverse events during follow-up peroid, indicating the persisted and high inflammatory property of CVD. Furthermore, new biosignaures and cytokines were found to related to future poor prognosis in CAD patients in addition to traditional biomarkers. Additionally, psychological personality as well as lifestyle factors also contributed to affect long-term outcome in patients with CAD.

**Conclusion:** The understanding of interactions of risk factors, environment lifestyle and psychological issue may help to elucidate the complex underlying mechanisms of CVD and help to identify patients at high risk of developing future adverse event, which may provide the individual and efficient treatment strategies for patients with cardiovascular disease.

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## 慢性B型與慢性C型肝炎健保給付抗病毒治療政策的演進與對健康的重大影響

## The Evolution of Reimbursement Policy for Antiviral Treatment Against Chronic Hepatitis B and C as well as Its Great Impact on Health

時 間：106年6月10日 13:30~18:00

Time：June 10, 2017 13:30~18:00

地 點：台北國際會議中心 102 會議室

Place：Conference Room 102
Taipei International Convention Center

# 慢性B型與慢性C型肝炎健保給付抗病毒治療政策的演進與對健康的重大影響

# The Evolution of Reimbursement Policy for Antiviral Treatment Against Chronic Hepatitis B and C as well as Its Great Impact on Health

# Translation of evidence-based research to a successful policy

# 將實證研究轉化為成功的政策

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Health policies usually involve a large number of subject or patient and, therefore, not only have to consider the efficacy but also the financial burden. A successful health policy must be cost-effective. To claim efficacy of a medical intervention, including survey, preventive measures and drug therapy, well-designed studies are needed. The best examples is the national universal HBV vaccination program in newborns based on demonstration of (a). perinatal and early childhood HBV transmission by prospective cohort studies and (b). the efficacy of HBV vaccination in newborns by randomized controlled trials. Based on earlier studies on the natural history of liver diseases, detection of small HCC and its doubling time, the national health provider has paid for HCC surveillance in subjects or patients at risk. As to antiviral therapy, various studies have provided evidence for the indication and timing to initiate drug therapy, the choice of the antiviral agent, the duration of therapy as well as how to monitor patients during and after therapy. In fact not all excellent evidence-based recommendations of major guidelines were followed by the policy makers, largely because of financial constraint. In this regard, new studies are needed to address the problems of the existing policy to persuade health authorities to revise the policy accordingly, as we have done in the past 1-2 decades. With these evidence-based health policies, the HBsAg carrier rate in the vaccinated population has decreased to <0.5%, the incidence and mortality of decompensation, liver cirrhosis and HCC have also significantly decreased in Taiwan. Conceivably, these successful evidence-based health policies have saved a lot of expense in the medical care and relevant surgical procedures for the patients with sequelae of advanced chronic liver diseases. In conclusion, translation of evidence generated from well designed research is crucial for a successful policy.

# The initiation of reimbursement policy for antiviral treatment against chronic hepatitis B and C

# 慢性 B 型與慢性 C 型肝炎健保給付抗病毒治療政策的源起

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Chronic viral hepatitis recently has become the leading infection disease and claimed about 1.3 million death a year in the world, surpassing the HIV. Effective treatment for chronic viral hepatitis B and C started to be available in the 1990s, as the interferon as the first regimen for CHB. A few years later, anti-HBV nucleot(s)ides were also approved in the developed countries. About the same time, the combination of interferon and ribavirin was shown effective in curing chronic hepatitis C, especially in Asia areas. Leaders of TASL and GEST realized the values of these regimens in reducing the CVH-related end-stage liver diseases and deaths, and continued trying to include these regimens into the National Health Insurance at earliest date. However, because of a high prevalence of CHB and CHC in Taiwan, the reimbursement would add a heavy financial burden impossible to maintain. Therefore the medical association worked out cost-effectiveness analysis to show its true impact on reducing death, and kept dialogues with BNHI. Other NGOs helped to raise the attention of the society for the unmet needs of many patients. Eventually, Both sides worked out the CHB/CHC reimbursement priority plan to initially treat the most urgent or most likely responsive patients to keep the budget under control from 2003. Afterwards, the coverage of CVH treatments was reviewed and then widened to cover more patients but still financially balanced. The step-by-step, incremental reimbursement plan has been shown practical in Taiwan. In fact, 14 years later, the age-adjusted liver-related death and HCC incidence rate dropped 10-15%, as compared to those in 2003.

The other approach, as highlighted in Australia or Spain for introducing direct antiviral agents (DAAs) for CHC therapy, is more aggressive. Both governments reached a deal with international pharmas to provide unlimited drugs for all CHC patients seeking therapies in the hospitals or clinics, at a ceiling budget about 10 billions of Australian dollars or Euros in five years. Such a sweeping strategy may produce a more rapid and dramatic impact, if proven by the outcomes in the next few years.

# The major revision of reimbursement policy for antiviral treatment against chronic hepatitis B and its impact on secondary and tertiary prevention of HCC

# 慢性 B 型肝炎健保給付抗病毒治療政策的重大修正及其對二級與三級肝炎防護的重大影響

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Hepatocellular carcinoma (HCC) is the second cancer mortality in Taiwan. Chronic hepatitis B (CHB) is the major etiology. A nation-wide reimbursement policy for CHB and chronic hepatitis C was initated since 2003, majorly revised in 2009 and further revised in 2016.

The major revisions included: (1) Use hepatitis B viral (HBV) load as a guideline because it correlates with the risk of liver cirrhosis and HCC. Liver biopsy is thus no longer required because it prevented many patients who are reluctant to this procedure from receiving reimbursed treatment. The criteria of HBV viral load for reimbursed treatment in HBeAg negative CHB patients is ≧ 2000 IU/ml and ≧ 20000 IU/ml for HBeAg positive patients. More than 260,000 patients have been benefited by this policy due to this revision. (2) The treatment duration was extended from 18 months to 36 months. If HBeAg seroconversion occurs at the end of treatment, it can be extended for another 12 months to consoidate the treatment efficacy since 2009. In 2016 revision, treatment duration can be indefinitely prolonged if HBeAg remains positive. Reimbursement course may be started again if clinical hepatitis relapses (CR) occur after discontinuation of nucleos(t)ide analogues (NA) from additional one course in 2009 to without limitation since 2016. Adequate treatment period reduces longterm sequale of cirrhosis and HCC and prevents CR-induced liver failure. (3) Patients with cirrhosis can be treated indefinitely. This revision reduces cirrhotic patients from progress to HCC or liver failure. (4) Treatment using NA with strong potency and high genetic barrier to replace the first generation NA with high rate of drug-resistance after prolonged treatment. (5) Rescue therapy using NA with high genetic barrier is provided for another 2 years if drug resistance occurs. The latter two criteria markedly reduce drug resistance and the associated virological and biochemcial breakthroughs to assure the treatment efficacy.

In summary, this reimursement policy has reduced HCC incidence, post-operate HCC recurrence and liver related-deaths. Our studies also show that if NA is given at the age <40 years old and non-cirrhotic stage, HCC patients with earlier HCC stages, the treatment efficacy is much better.

# The major revision of reimbursement policy for antiviral treatment against chronic hepatitis C and its impact on secondary and tertiary prevention of HCC

# 慢性 C 型肝炎健保給付抗病毒治療政策的重大修正及其對二級與三級肝癌防護的重大影響

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Hepatitis C virus (HCV) infection is a major health problem throughout the world. The estimated prevalence of HCV infection is around 3% in Taiwan. Approximately 700,000 people are infected with HCV. Among them 550,000 are with chronic HCV infection. Chronic hepatitis C (CHC) will lead to liver cirrhosis (LC) and hepatocellular carcinoma (HCC). The goals of the treatment for hepatitis C are to decrease the infectivity, decrease the risk for cirrhosis or decompensation, decrease the development of HCC, and improve the survival and quality of life of the patients. For the secondary and tertiary prevention of chronic liver diseases and hepatocellular carcinoma, the Taiwan National Health Insurance reimbursed the treatment for chronic HCV infection since October 2003. Pegylated interferon (pegIFN) and ribavirin (RBV) were used. The sustained virologic response (SVR) rates are 70 to 80% in genotype 1 CHC patients and around 90% in patients with genotype 2 CHC. SVR by interferon-based therapy could decrease the disease progression to liver cirrhosis (The 15-year cumulative incidence of cirrhosis decreased from 36.6% in untreated patients to 4.8% in patients with an SVR), reduce the risk of HCC development (the cumulative incidence of HCC decreased from 35.2% in untreated patients to 3.0% in patients with an SVR), and improve the survival of the patients (the cumulative incidence of survival increased from 93.1% in untreated patients to 99.0% in patients with an SVR). Data analysis based on the Taiwan's National Health Insurance Research Database showed that postoperative pegIFN/RBV treatment was associated with reduced recurrence of HCV-related HCC and improved survival of patients with HCV-related HCC. New combination therapies with direct-acting antivirals (DAA) have the characteristics of high SVR rates, low toxicity, good tolerability, short duration, high barrier to resistance, and low drug-drug interactions. Since January 24th 2017, the Taiwan National Health Insurance reimbursed the DAAs treatment for chronic HCV infection. More patients will be benefited by the new reimbursement policy.

# The impact of reimbursement policy for antiviral treatment against chronic hepatitis B and C on extrahepatic manifestations of viral hepatitis

# 慢性 B 型 C 型肝炎健保給付抗病毒治療政策對病毒性肝炎肝外表現的影響

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Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) are established causes of liver diseases including chronic hepatitis, cirrhosis, and hepatocellular carcinoma. In addition to liver problems, several extrahepatic manifestations of chronic HBV or HCV infections have been investigated. Using Taiwanese data, chronic HBV infection was shown to be associated with increased risk of intrahepatic cholangiocarcinoma and non-Hodgkin lymphoma (especially the subtype of diffuse large B-cell lymphoma) in a nationwide cohort of pregnant Taiwanese women. The REVEAL-HBV cohort study showed that chronic hepatitis B was associated with an increased risk of pancreatic cancer. In addition, mortality rates from circulatory diseases, kidney diseases, esophageal cancer, prostate cancer, and thyroid cancer, as well as incidence of type II diabetes were increased in patient with chronic HCV infection than those who did not infect as shown in the REVEAL-HCV cohort.

Using the Taiwan National Health Insurance Research Database (NHIRD), HBV infection has been shown to be associated with increased risk of colorectal cancer, gallbladder and extrahepatic bile duct cancer, pancreatic cancer, kidney cancer, ovarian cancer, non-Hodgkin's lymphoma, and rheumatoid arthritis. In the same database, chronic HCV infection was shown to be significantly associated with an increased risk for gallbladder and extrahepatic bile duct cancer, ovarian cancer, non-Hodgkin's lymphoma, early-onset breast cancer, and rheumatoid arthritis. Antiviral treatment for HCV using pegylated interferon plus ribavirin was associated with improvements in end-stage renal disease, acute coronary syndrome, and ischaemic stroke, but not in autoimmune diseases. In diabetic patients, interferon-based antiviral treatment for HCV was also associated with improved renal and cardiovascular outcomes.

Further studies investigating effects of antiviral therapies on reported extrahepatic manifestations using NHIRD or national databases such as Cancer Registry are warranted.

# The need of direct-acting antiviral (DAA) for the treatment of chronic hepatitis C and its impact on health

# 直接抗病毒藥物的需要及其對健康的影響

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Hepatitis C virus (HCV) infection is of growing international concern because of the substantial effect on morbidity and mortality. A leading cause of cirrhosis, hepatocellular carcinoma (HCC), liver transplantation and liver-related death worldwide including Taiwan. The disease inflicts an immense health and economic burden in Taiwan due to the infection's hepatic and extrahepatic effects.

In 2016, the 69th World Health Assembly approved the Global Health Sector Strategy to eliminate hepatitis infection by 2030, and WHO introduced global targets for the care, and management of HCV including " a 90% reduction in new cases of chronic hepatitis C, a 65% reduction in hepatitis C deaths, and treatment of 80% of eligible people with chronic hepatitis C infections." To achieve these goals, we need to develop national policies based on up-to-date, reliable epidemiological evidence and a new therapeutic strategy.

The prevalence of anti-HCV in general population in Taiwan is 4%. The calculated infected Patients is 0.75 million. Of them, 0.55 million (~75%) were HCV viremic and need antiviral therapy. The national health insurance has reimbursed ribavirin plus pegylated interferon therapy to treat chronic HCV infected patients since 2003. Uptoday, there are only 0.1 million patients received ribavirin plus pegylated interferon therapy with a sustained virological response (SVR) rate of ~70% regardless of HCV genotype. The reasons of lower treated numbers were due to ineligible (~18%), intolerable (~18%) and fear of side effect (~37%) of ribavirin and pegylated interferon therapy. Therefore, we urgently need direct antiviral agents (DAA) to treat chronic HCV infected patients in Taiwan not only the lower side effects (<20%) but also the higher SVR rate (~98%).

Additionally, an estimated model between numbers of treated patients and the health impact has demonstrated if we increase the treatment numbers from present 8000 to 33970 in 2020 and persist to 2030, then the total new infection patients will decrease 98%, the hepatic decompensation will decrease 80%, HCC decrease 79% and liver related death decrease 90%. Obviously, we need DAA to treat HCV infected patients and gradually increase the treatment numbers to 34000. Hopefully, we can achieve WHO introduced global targets and the Global Health Sector Strategy to eliminate HCV infection by 2030.

# Unmet needs of reimbursement policy for treatment against chronic hepatitis B and C

# 慢性 B 型 C 型肝炎健保給付抗病毒治療政策尚待改進之處

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WHO proposes “Global targets to be achieved if viral hepatitis is controlled by 2030”: (1) 90% reduction in new cases of chronic hepatitis B and C; (2) 80% of treatment eligible people with chronic hepatitis B and C be treated; and (3) 65% reduction in hepatitis B and C-related deaths. To achieve the goals proposed by WHO, awareness of the liver diseases in general population, accessibility to medical care for patients infected with hepatitis B or C, availability of effective antiviral therapies, and affordability of the patients and the government will be of tough and priority issues to be resolved worldwide including Taiwan. Through decades of development, there are several new and potent antiviral agents available for the treatment of chronic hepatitis B or C. As for chronic hepatitis C virus (HCV) infection, in the era of interferon-free direct acting antivirals (DAAs), international guidelines (including AASLD, EASL and WHO) suggest that treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. The main difficulty for the generalization of DAAs is the high cost. In contrast, for chronic hepatitis B virus (HBV) infection, we do not have agents for the cure of the virus infection. Thus, different treatment recommendations exist regarding the indication, duration and stopping criteria for patients with HBeAg-positive or -negative chronic hepatitis B.

Overall, there are unmet needs in current screening and reimbursement policies for patients with chronic viral hepatitis B and C in Taiwan. First, for chronic hepatitis B, more clinical trials/studies are needed to provide evidence-based country-tailored recommendations. For example, how long should we treat patients with HBeAg-negative chronic hepatitis B using anti-HBV oral nucleos(t)ide analogue therapy? Fixed duration post negativity of serum HBV DNA? Or till loss of HBsAg? When should we start to treat patients with different stage of liver fibrosis? As for the treatment of chronic hepatitis C using DAA-based therapy, the main issue is the negotiation among government decision makers, pharmaceutical companies and the medical society in order to provide effective, safe and affordable DAA therapy to all HCV-infected subjects. Most importantly, the government budget should be increased and secured. Infrastructure for screening, diagnosis and referral of patients infected with HCV or HBV should be developed at the same. And health care manpower should be expanded to tackle the big burden of patients to be managed in the near future.

# Patient value-based medicine: To search for better patient care in real life

# 病人價值為本的醫療：在現實生活中尋求更好的病人照顧

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The Taiwan national health insurance (NHI) system was created in 1995 to promote high quality health care for all citizens. In order to develop patient-centered holistic care, pay for performance plan was applied for chronic Hepatitis B virus (HBV) carriers and Hepatitis C virus (HCV) infected patients since 2010.

Reimbursement for HBV/HCV patients was enhanced to a 3-year anti-viral therapy conducted with precise serum HBV/HCV DNA level assay. Recently, NHI expands treatment protocol with life-long therapy for HBV based on the patients' clinical status. Furthermore, we also started to supply anti-HCV oral medication therapy with 2 billion NT dollars budget from 2017.

NHI HBV/HCV reimbursement policy was a role model of payment for patient value-based medicine. Facing the hike of health care expenditures, NHI still have to introduce more cost-effective innovative medicine as good health services. With the development of precision medicine and limited NHI budget, these value-based medicine should be determined by patient's treatment outcome and total cost through the specialist committee. NHI aim is to encourage health care providers to integrate services to save unnecessary medical service cost and offer reward innovative new technologies to create high quality medical service.

為了增進全體國民健康，全民健保於 84 年成立。自開辦以來，全民健保為提供病人優良的醫療服務品質，持續透過調整支付醫療費用的方式，提供適當誘因，引導醫療服務提供者朝向以病人為中心的整體性醫療照護發展，並以病人醫療品質及成效作為費用支付的依據，自 90 年 10 月起，分階段實施醫療給付改善方案，其中慢性 B 型肝炎帶原者與 C 型肝炎感染者論質方案，即於 99 年 1 月開始實施。

配合 B、C 肝論質方案，健保於 98 年 11 月 1 日放寬對慢性 B 、C 型肝炎治療之給付規範，不但採用血中 HBV DNA 或 HCV RNA 病毒量之測定取代肝穿刺及病理檢查，給付期間也延長至三年。而考量慢性肝炎病人需長期用藥的需求，健保對 B 型肝炎病毒相關之肝硬化患者提供長期之口服抗病毒藥物治療，今（106）年 1 月 1 日起更放寬 B 型肝炎治療之給付規範，只要符合規定，給付期間不再限療程次數。至於 C 型肝炎口服新藥，健保亦於 106 年 1 月 24 日起開始給付，106 年度健保總額匡列 C 型肝炎口服新藥專款費用約 20 億元，並以包裹給付方式 ( 每療程 25 萬新台幣 ) 克服經費不足的困難。

健保 B、C 肝論質方案及 C 型肝炎口服新藥給付方式，正是以病人價值為本之醫療的闡釋。面對醫療費用不斷提升的挑戰與難題，台灣與部分歐洲國家都已積極導入以科學實證的醫療科技評估方式，分析新藥與新醫療服務之經濟效益，以病人疾病的完整照護週期作為單位來衡量結果與成本，也就是對病人的價值評估。而隨著精準醫療發展，病人價值的考量應加重不同族群、不同疾病的差異性與社會成本的考量，藉以鼓勵醫療照護提供者整合服務以節省成本，並提供保險人據以建立合理健保給付的依據，同時適度回饋新醫療科技的發展者，創造多贏的局面。

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## 三維列印技術與導航系統於外科手術的應用

## 3D Printing Techniques and Surgical Navigation in Surgery

時 間：106年6月10日 13:30~17:30

Time：June 10, 2017 13:30~17:30

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Place：Conference Room 105
Taipei International Convention Center

# 三維列印技術與導航系統於外科手術的應用

# 3D Printing Techniques and Surgical Navigation in Surgery

# Computed navigation system in spine surgery

# 電腦導航系統應用於脊椎手術

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Minimally invasive approaches are increasingly being used in various spinal disorders, such as degenerative spine, trauma, and tumors. The purpose of this study is to review and report our experience using intraoperative O-arm navigation in the treatment of long segment spinal instrumentation.

We retrospectively reviewed patients who underwent posterior spinal instrumented fusion for more than 4 levels and using intraoperative O-arm navigation for percutaneous pedicle screw insertion. Screw placement and deviation were evaluated by O-arm scanning immediately. Total operation time including screw insertion time and rod insertion time were recorded. Clinical and radiological results were reported as well.

From January 2016 to December 2016, 8 consecutive patients with neurological deficit were included. The primary diagnoses were burst fracture (5), chance fracture (1), metastasis (2),and multiple discitis (1). There were 5 males, and 3 females with mean age of 61.6 years. 83 pedicle screws were placed in these patients with 24 over thoracic spine, and 59 over lumbar spine. There was no visceral or neurovascular injury. However, 3 pedicel screws malposition were noted and corrected immediately. Mean operation time was 3.6 hours including mean O-arm guided screw placement for 2.5 hours and mean rod insertion for 1.1 hours.

Minimally invasive long segment pedicle screw insertion assisted by O-arm navigation with acceptable accuracy was noted. Contouring and insertion of the rod is challenging, however, O-arm assisted long instrumentation with short decompression and fusion is efficient and safe with minimal morbidity.

# Interdisciplinary 3D planning for orthognathic surgery

# 三維列印技術於正顎手術整合性計畫

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Conventional paper and model surgery remains the most widespread and standard method by which surgical planning is achieved. Detailed approaches to plan these cases have also been described using cephalometric and occlusogram predictions. However, the limitation of these conventional techniques results from using 2-dimensional tools to attempt accurate prediction of 3 dimensional surgical and orthodontic movement. Moreover, conventional planning techniques do not provide a final 3-dimensional (3D) visual treatment objective to further guide surgical and orthodontic precision.

Computer aided surgical simulation (CASS) utilizing 3D images obtained from multi-slice computer tomography (MSCT)/cone beam computer tomography (CBCT) has been successfully performed previously to plan craniofacial surgery. By substituting the dentition in MSCT/CBCT images with images acquired from surface laser scanning of dental models, we can virtually construct a composite skull model that can be used for accurate diagnosis, planning, and simulation not only of the facial skeleton but equally well for orthodontics.

The development of CASS represents a paradigm shift in surgical planning for patients with craniomaxillofacial deformities. Dr. Jaime Gateno and Dr. James Xia have developed a CASS based surgical planning protocol (CASS planning protocol) for orthognathic surgery. In this protocol, a computerized composite skull model of a patient is generated to accurately represent the facial soft-tissue, the skeleton and the dentition. In addition, a patient's neutral head posture is recorded on the patient and transferred to the 3D models. Afterwards, the physician performs virtual osteotomies and move skeletal segments to simulate orthognathic surgery. Finally, surgical splints and/or templates are generated accordingly and utilized in surgery to accurately position the osteotomized bony segments.

The CASS planning protocol improves clinical practice a lot. First, physicians can foresee the possible problems during the surgery so be prepared in advance. In addition, output the stereolithographic model in CASS planning protocol make pre-bending plates and templates of the bone graft possible, reducing operation time and improving patients' recovery postoperatively. Otherwise, a better treatment alternative can be developed because of the visualization of the whole treatment procedures and results that provides a wonderful platform for communication between surgeons, orthodontists, other specialties, and even patients. At last, comparison of planned and actual outcome images also reveals the direction and amount of the surgical errors, serving as the quality control of the orthognathic surgery. Several clinical cases of mandibular prognathism, facial asymmetry, obstructive sleep apnea (OSA) will be shown for explanation in the presentation.

# Multifariously combined use of virtual image manipulation and physical model fabrication in craniofacial reconstructive surgery

## 利用電腦模擬三維影像設計加上實體模型輔助顱顏重建手術

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For particularly challenging craniofacial reconstruction cases with perplexing derangements involving both soft and hard tissue components, the formulation and execution of a comprehensive, precise surgical plan is imperative.

The computerized imaging and virtual planning not only permits unlimited sessions of pre-operative trials but may also provide vivid foresight of the facial outlook in high fidelity layout. Traditional physical dental cast model surgery, on the other hand, remains the gold standard of assessment method for dental occlusal interrelationship. In this report, we present our approach of seaming up the technologic gap in between these two different systems and working out a comprehensive pre-surgical planning program.

In short, virtual osteotomy is performed in the computer. The plaster model and the facial bone image are synchronized using a simple optical tracking device, so that when the dental model is mobilized, the jawbones move accordingly in the computer at the same time. As such, every spatial movement of the physical dental cast model can be translated and incorporated into the virtual computerized image. By doing so, we can negotiate between optimal occlusion and optimal symmetry.

The integrated system is able to achieve desirable facial contour with simultaneous establishment of acceptable and stable occlusal relationship. The reduction of uncertainty in turn contributes to a more assured, expedient and safer surgical undertaking.

In addition to that, a creative use of physical guiding models will greatly facilitate of the reconstructive effort by enhancing its accuracy and certainty.

# Surgical navigation system in craniofacial surgery

## 手術導航系統在顱顏手術方面的應用

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The complex nature of the craniomaxillofacial structures challenges the surgeon's knowledge to anatomy, experience, and the perception toward surgical outcome. Especially in facial traumatic injury, how to restore the facial contour and function is the utmost treatment goal. With the rapid development of digital technologies in recent decades, the computational algorithm, modeling/navigation techniques profoundly change the surgical practice in different surgical specialties. Not surprisingly, the combination of virtual surgical planning, three-dimensional printing techniques, and surgical navigation becomes an emerging trend in contemporary craniomaxillofacial surgery. Volume rendering from different image sources allows the surgeon to analyze the patient in three-dimensional format and to manipulate deformed or missing facial structures by computational algorism such as mirroring, segmentation, or insertion of unaltered or ideal skeletal constructs. The execution of the virtual planning is then accomplished by using stereolithographic models (SLMs), implants, cutting guides, or through image-guided surgery in the form of intraoperative navigation. Computer-assisted surgery become an umbrella term that encompass these associated techniques. By the literature review, the perceived benefits of those "computer-assisted surgery" are increased surgical precision, improved operative efficiency, and overall good outcomes. However, we are hardly to see the ideological process or reflections of the transition toward computer assisted surgeries. Computer-assisted surgery is constantly applied on traumatic, oncologic, and orthognathic cases nowadays. In this talk, I will share our clinical experience on practicing computer-assisted approach in cranio-maxillofacial surgery.

# Change of pelvic fracture management workflow in a trauma center following the use of 3D navigation-guided minimally invasive surgery fixation (MIS) of pelvic-acetabular fracture

## 骨盆三合一創傷控制療法及電腦導航微創內固定的應用

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The 3-in-1 exsanguinating pelvic fracture protocol (3-in-1 protocol) has been implemented in our center since 2008. Significant improvement in survival rate of patients with unstable pelvic fracture was observed from 27% before 2008 to 76.2% in 2015. This increased survival means more severely injured patients requiring definitive fixation, resulting in increased clinical experience in both open reduction internal fixation (ORIF) and x-ray guided minimally invasive screw fixation (MIS) for pelvic-acetabular fracture. Fixation strategy for different fracture patterns using different screws was also standardized. 3D navigation MIS was developed since October 2015 to further facilitates the MIS technique.

For non-displaced or minimally-displaced fracture, CT pelvis DICOM taken after trauma activation were imported to navigation computer, which allowed assessment of screw fixation feasibility and detailed planning of length and trajectory of screws for different fracture patterns. If the fracture patterns were not feasible for navigation MIS due to fracture displacement, those with 3-in-1 protocol would receive close or open reduction in the same operative session as removal of pelvic packing, followed by repeating pelvic CT to assess feasibility of navigation MIS; those displaced fractures without 3-in-1 protocol would receive fracture reduction under general anaesthesia followed by intra-operative 3D assessment, planning and execution of MIS fixation in the same operative session. This new workflow aims at making every pelvic-acetabular fracture feasible for 3D navigation MIS until proven otherwise. This allowed most complex pelvic acetabular fractures to be treated by 3D navigation MIS instead of traditional ORIF.

Previously, definitive pelvic-acetabular fixations were usually performed after patients were absolutely stabilized and discharged from the Intensive Care Unit. With the modified pelvic fracture workflow, most definitive pelvic-acetabular fixations were performed earlier, when the patients were relatively stable in the Intensive Care Unit.

From October 2015 to September 2016, 35 consecutive pelvic-acetabular fracture with different complexity indicated for surgery admitted to our center were reviewed. Three (9%) required ORIF because of pubic symphyseal diastasis and posterior acetabular wall fracture with hip instability. The remaining 32 patients (91%) were treated using 3D navigation MIS. Among these 32 patients, the average age was 52.9; 78% had trauma activation; 47% had received 3-in-1 protocol; the average Injury Severity Score was 21.8; 43% and 9% had received close and open reduction respectively to make 3D navigation MIS feasible on displaced fractures; the average duration from injury to definitive fixation was 5.5 days.

There were 119 screws inserted under 3D navigation, including 45 sacroiliac screws, 41 retrograde anterior column screws, 28 supra-acetabular screws, three antegrade posterior column screws and three

sub-cristal screws. The average operative time was 148 minutes; the average intra-operative blood loss was 197ml, which was significantly lower than traditional ORIF that required extensive surgical exposure. There was no surgical complication. The average entry and tip deviation (accuracy) between the planned and executed screws measured in the navigation computer were 2.11mm and 2.19mm respectively; part of the deviations were explained by our joystick closed reduction technique for displaced fragments upon guide-pin insertion, which is in fact beneficial to fracture reduction. However, such deviations could still be a potential risk in cases of small pelvis, displaced unstable floating fragments, and in surgeons with less experience. A robot-assisted navigation may be a potential direction for future development with less deviation. Fracture union and functional outcome of this group of patients will be updated.

In conclusion, 3D navigation MIS in conjunction with detailed pre-operative planning, appropriate fracture reduction maneuver and standardized screw fixation strategy allow early definitive fixation for simple and complex pelvic-acetabular fractures in a less traumatize way to the already traumatized patients.

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## 眼科專家與跨領域專家對談

## Talk between Eye Specialist and Cross-field Experts

時 間：106年6月10日 13:30~17:30

Time：June 10, 2017 13:30~17:30

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Place：Conference Room 201A
Taipei International Convention Center

# 眼科專家與跨領域專家對談
# Talk between Eye Specialist and Cross-field Experts

# Ocular adnexal tumors and inflammatory disease: Beyond surgery and chemotherapy

## 眼部腫瘤或發炎性疾病除了手術及藥物治療外，還能為病患做什麼？

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**蔡傑智**

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Radiotherapy can be used to maintain vision by avoiding sacrifice of useful ocular tissue to obtain local control in malignant ocular tumors. External beam radiotherapy is the most common. It can be used alone or together with surgery or chemotherapy. In addition, we have successfully used adjunctive orbital radiotherapy for the treatment of refractory ocular inflammatory disease. Our study shows it helps to achieve stable disease and cessation of systemic corticosteroid in patients with refractory ocular adnexal IgG4-related disease and Graves' ophthalmopathy.

The main concern with radiotherapy is damage to parts of the eye, leading to problems such as dry eyes, cataracts, neovascular glaucoma, radiation retinopathy, and optic neuropathy. Radiation works on cells by creating free-radicals which can directly destroy cells and by breaking cellular DNA, leading to short term and long term side effects. The risk depends on the size and location of the tumor, the dose given, the age of the patient, or other synchronous diseases. In addition, orbital anatomy and ocular radiosensitivity provide unique challenges for radiation therapy. Especially, there exists a spectrum of radiation tolerance among normal ocular tissues. For example, whereas orbital bones, muscle, and fat can tolerate relatively high doses; the lens, eyelashes, retina, optic nerve, and lacrimal system are more radiosensitive.

However, radiotherapy remains to play an indispensible role in the treatment of ocular adnexal tumors and inflammatory disease. This is because the clinical benefits of improving survival and preserving vision clearly outweigh the risks. To maximize control of disease and to prevent and reduce the risk of radiation sequelae remains the primary goal of any radiotherapy plan.

# Radiotherapy for ocular adnexal tumors and inflammatory disease

## 眼部腫瘤或發炎性疾病的放射治療

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Radiotherapy has been widely used for the treatment of orbital tumors and inflammatory disease. Nowadays, when most patients are treated by linear-accelerator-derived external beam photon radiation therapy, other modalities, including Gamma-Knife Radiosurgery, proton, and heavy-ion therapy have become more available in developed countries. With careful treatment planning, radiotherapy brings excellent treatment outcome with mild toxicity. Major indications, including ocular melanoma, orbital and intraocular lymphomas, thyroid ophthalmopathy, and orbital pseudotumor, will be reviewed. The tolerance of normal ocular and orbital tissues are reported. We will also cover ophthalmic radiation side effects to each site.

# Keratopathy in patients with Hema/Onco/Immune diseases

## 角膜潰瘍不好，全身血液腫瘤免疫問題一堆，怎麼辦？

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Management of keratopathy in patients with hematology, oncology, and immune diseases is more troublesome. Cornea surgeons may encounter tough situations that require consultation with physicians of internal medicine. In this speech, I will present cases to raise the following issues:

1. Are there indices to grade risks of surgery in patients with leukopenia or thrombocytopenia secondary to chemotherapy or hematology diseases? What are the indications of blood transfusion? Are 2nd line antibiotics indicated? For patients requiring eye surgery and further chemotherapy, what is the best way of mutual cooperation in respect of timing of surgery, supplement pre- and post-operative management, specific parameter to monitor risks, etc.?
2. Peripheral ulcerative keratopathies can be idiopathic or associated with autoimmune diseases including rheumatoid arthritis, SLE, etc. Progression of cornea pathology is not necessarily associated with progression of systemic manifestations. What systemic immuosuppressants benefit most to patients with poor response to local eye treatment? What are their common side effects and how to monitor and prevent them? Are there specific regulations for prescribing these drugs? Is it safe for an ophthalmologist to prescribe these drugs? If not, what is the best way of mutual cooperation?
3. What is the general management of GVHD? Will that be different in cases with ocular GVHD? What are the risks of eye surgery in patients with GVHD? Are there pre- and post-operative managements to reduce the risks?
4. We are seeing increasing number of patients with keratopathy secondary to target therapy with EGFR inhibitors. Can these drugs be stopped in patients non-responsive to eye local treatment? If yes, for how long? Are there any other substitutes? Patients usually need to take these drugs for how long?

# Common ophthalmological manifestations of hemato-oncological diseases

# 血液腫瘤疾患常見的眼科徵兆

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Ocular manifestations are important presentations of hematological and oncological diseases. However, negligence may sometimes occur due to the unfamiliarity of hematologists/oncologists to the ophthalmologic presentations. The causes of ophthalmological manifestations of hemato-oncological diseases include primary intraocular tumors, direct invasion of tumor tissues or infiltration of malignant cells into the intra-ocular structures, cancer-associated coagulopathies, and opportunistic infections due to immunocompromised status of patients.

In this presentation, I will discuss the common manifestations of hematological diseases and oncological diseases. For hematological diseases, intra-ocular hemorrhage due to bleeding diathesis, thrombotic events due to macroglobulinemia or leukemia-induced hyperviscosity, opportunistic infections such as CMV retinitis, toxoplasmosis, and fungal infection due to immunocompromised status of patients, leukemic infiltration of different intraorbital regions, lymphoma from mucosa-associated lymphoid tissue (MALToma), mycosis fungoides of eyelids, ophthalmological manifestations of graft-versus-host diseases (GVHD) in patients receiving allogeneic stem cell transplants, and steroid-induced cartaract will be discussed. For oncological diseases, intra-ocular metastasis, intraocular hemorrhage or thrombotic events caused by cancer-associated disseminated intravascular coagulopathy, primary uveal melanoma and melanoma from eyelids, optic nerves compression caused by intracranial invasion of solid tumors, oculomotor disabilities caused by intracranial invasion of solid tumors, and keratitis caused by herpes zoster involved in the dermatome of trigeminal nerve, will be discussed.

In summary, alertness of hemato-oncologists to the ophthalmological manifestations and a close collaboration between hemato-oncologists and opthalmologists are essential for the diagnosis and improving the treatment outcome of these relatively usually but important events of cancer patients.

# Ocular manifestation of carotid-cavernous fistula

## 頸動脈海綿竇廔管之眼部徵狀

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Carotid-cavernous fistula (CCF) is a type of arteriovenous fistula resulting from an abnormal communication between the arterial and venous systems within the cavernous sinus. It may occur spontaneously or after an episode of head trauma, surgical injury, aneurysm rupture. There are different classifying systems for CCF depending on the flow rate (low-flow or high-flow), etiologies (traumatic or spontaneous) and anatomical characteristics (direct or indirect). CCF may present with various manifestations such as red eye, proptosis, diplopia, progressive visual loss, high intraocular pressure, headache, orbital pain, tinnitus…etc. Non-invasive neuroimaging studies of CT and MR imaging may help to provide evidence of CCF such as enlarged superior ophthalmic vein, increased thickness of extraocular muscles, proptosis of eyeball, and increased flow-void in the cavernous sinus. Diagnosis relies on the cerebral digital subtraction angiography (DSA) which may help to visualize the fistula.

# Endovascular management of carotid-cavernous fistula

## 經血管路徑處理頸動脈 - 海綿狀竇廔管

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Carotid-cavernous fistula (CCF) is a fistula between carotid artery and cavernous sinus. Most CCFs presented with neuro-ophthalmic symptoms such as ocular-orbital venous congestion, cephalic bruit and/or impairment of cranial nerves. CCFs were classified into direct or indirect type depended on fistula anatomy.

Direct CCF (DCCF) is a direct connection of high-flow cavernous internal carotid artery (ICA) to low-flow cavernous sinus, usually resulting from trauma or ruptured cavernous ICA aneurysm. Trans-arterial coil embolization is the standard method to manage DCCF with promising results. The angiographic cure with preservation of the flow of ICA can be achieved in 70-80% of aptients; however, about 20-30% DCCFs, the affected ICAs have to be occluded to treat the DCCF because of large tear or transection of ICA. Major complication of endovascular embolization of DCCF is thromboembolic events, it occurred in less than 3% of patients.

Indirect CCFs, also called cavernous sinus dural arteriovenous fistulas (CSDAVFs), are arteriovenous fistulas of the cavernous sinus (CS), fed by dural branches of internal and/ or external carotid arteries. Most CSDAVFs are low-flow shunts, fed by dural branches of external or internal carotid artery. Indirect CCFs usually presented with benign orbital chemosis, and/or impairment of visual acuity. Transvenous coil embolization of cavernous sinus is the preferred method to manage the indirect CCF. The cure rate by transvenous route can be achieved in 80-90% patients. Few indirect CCFs with few dural feeders can be accessed via arterial route with liquid embolic agent embolization. The major complications of endovascular embolization such as hemorrhagic or non-hemorrhagic stroke are less than 3% by experienced operators.

Endovascular embolization is an effective and safe method to manage CCFs with promising outcomes. The selection of access routes and embolic materials are depended on fistula anatomy.

# Management of diabetic retinopathy: Stopgap approaches?

## 糖尿病視網膜病變的處理：頭痛醫頭，腳痛醫腳？

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Diabetic retinopathy is one of the microvascular complications of diabetes. Vascular ischemia, leakage and inflammation are three interplaying mechanisms for the systemic complications as well as the retinopathy. It was well known that strict glycemic control, blood pressure lowering, and statin use for hyperlipidemia were associated with less risk of progression of retinopathy. However, when dealing with management of vision threatening retinopathy such as diabetic macular edema or proliferative retinopathy, what is the role for controlling the systemic risk factors? For example, will the glycemic control add on the outcome of anti-VEGF intravitreal injection for macular edema? Will the lipid lowering drugs decrease the lipid exudate from the retinal microaneurysms? How was the renal function affecting the macular edema? Shall we stop or modify anti-coagulants use for diabetic patients with new onset vitreous hemorrhage who had history of ischemic heart disease or stroke? What other systemic signs should we care about and how to work together with the metabolic doctors in managing the patients?

This talk will post questions of cases with diabetic retinopathy and ask opinions from the metabolic doctor for their comprehensive approach for the patient. It was hoped that through the interacting Q and A and discussion from both ophthalmologist and diabetologist, the audience will have an idea on how to manage the retinopathy not only based on ophthalmic clinical trials, but also on update trials and systemic management given by our internal medicine partners.

# Diabetes control and retinopathy

## 糖尿病控制不好和眼睛 ( 視網膜 ) 有甚麼關係？

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Diabetes is a group of metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion and insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs. Diabetic retinopathy is a highly specific complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control. It is strongly evidenced that the normal blood glucose level is defined based on the retinopathy.

Several decades before, the blood glucose levels were found to be correlated with retinopathy: the higher the blood glucose levels, the higher the prevalence of retinopathy. There are growing evidences that diabetes control, including blood glucose and blood pressure, could decrease the new onset and progression of retinopathy. The most famous randomized control trials for diabetes control and retinopathy were DCCT (Diabetes Control and Complication Trials) in type 1 diabetes and UKPDS (United Kingdom Prospective Diabetes Study) in type 2 diabetes.

Diabetic retinopathy is classified into two stages: nonproliferative and proliferative. Nonproliferative diabetic retinopathy usually appears late in the first decade or early in the second decade of the disease. Mild nonproliferative retinopathy could progress to more extensive diseases. Diabetes is the leading cause of blindness in the working age. Blindness is primarily the result of proliferative diabetic retinopathy and clinically significant macular edema.

High quality fundus photographs can detect most clinically significant diabetic retinopathy. However, dilated and comprehensive eye examination by an ophthalmologist should be performed at the time which patients are diagnosed with type 2 diabetes, or 5 years after the diagnosis of type 1 diabetes. The screens for retinopathy should be performed annually. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated by an ophthalmologist and follow-up's closely.

The role of endocrinologist or diabetologist is to control blood glucose and blood pressure to optimal levels, perform screenings for retinopathy and, if necessary, early referrals to ophthamologists.

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## 提升重病者生命品質
## 並提供其高價值的緩和醫療

# Improve Quality of Life and Provide High-Value Palliative Care for the Seriously Ill Patients

主辦單位：中華醫學會
協辦單位：臺北榮總家庭醫學部/退輔會北區榮民安寧緩和資源中心

**時 間：106年6月10日 13:30~17:30**
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**地 點：台北國際會議中心 201B 會議室**
**Place：Conference Room 201B**
**Taipei International Convention Center**

# 提升重病者生命品質並提供其高價值的緩和醫療
# Improve Quality of Life and Provide High-Value Palliative Care for the Seriously Ill Patients

# Transforming care for the seriously ill: The role of modern palliative care

# 重病者照護之轉變：現代安寧療護的角色

**Rolfe Sean Morrison**

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The elimination of suffering and the cure of disease are the fundamental goals of medicine. While medical advances have transformed previously fatal conditions such as cancer and heart disease into illnesses that people can live with for many years, they have not been accompanied by corresponding improvements in the quality of life for these patients and their families. Living with a serious illness should not mean living in pain or experiencing symptoms like shortness of breath, nausea, or fatigue. Yet, multiple studies over the past decade suggest that medical care for patients with serious illness is characterized by inadequately treated physical distress; poor communication between doctors, patients, and families; and enormous strains on family caregiver and support systems. In this talk, I will discuss how modern palliative care can improve outcomes for seriously ill patients and families; improve satisfaction with care, and lower costs. I will discuss existing models of palliative care delivery and also address new models of care to extend services beyond the hospital and into the community where most patients would prefer live. Finally, I will focus specifically as to why palliative care is different form end-of-life care and the need to provide it at the same time as all other life-prolonging and curative treatments.

# A good death: Facilitating end-of-life care decisions that honor patients' wishes

## 促進臨終照顧決策決定以達如末期癌症病人所願之善終

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Improving the quality of end-of-life (EOL) care to facilitate a good death for terminally ill cancer patients has become a major agenda and has been named as a national priority around the world. U.S. Institute of Medicine advocates a good death that is “in accord with the patients’ and families’ wishes.” Adequate knowledge of the prognosis is a prerequisite for planning appropriate EOL care, thus improving EOL-care quality by limiting potentially futile anti-cancer and life-sustaining treatments (LSTs) to avoid unnecessary suffering, improve one’s quality of life (QOL), and promote care in line with one’s values and wishes. In addition, aligning clinical practices to patients’ values, goals, and preferences for EOL care to “personalize” this care requires effective physician-patient discussions. However, our previous data demonstrated great discrepancies between patients’ preferred prognostic information and actual prognostic disclosure with only a minority of terminally ill cancer patients being aware of their prognosis and EOL-care discussions remain exceptional. Furthermore, Taiwanese families have the duty and authority to make medical decisions on behalf of their terminally ill members. However, our previous national survey showed great disagreement between patients’ and family caregivers’ preferences for EOL care. In this presentation, given there is substantial growth in the hospice/palliative care movement in the past decade in Taiwan, which emphasizes respecting patient wishes and avoiding LSTs that are non-beneficial, changes in the extent of prognostic awareness, EOL-care discussions, and agreement between cancer patients’ and family caregivers’ preferences for EOL care over a decade will be first presented.

Second, our previous nationwide surveys used a cross-sectional design, which cannot capture dynamic changes in terminally ill cancer patients’ prognostic awareness, discussions of their EOL care with their physician, and preferences for EOL care in response to worsening physical symptoms and possibly diminished family resources as death approaches. The extent to which patients’ preferences for EOL care are honored may be distorted if preferences are measured long before death. Furthermore, accurate prognostic awareness and physician-patient discussions may facilitate terminally ill cancer patients’ coming to terms with their forthcoming death and making realistic and value-consistent EOL care decisions, but may also lead to emotional and existential/spiritual distress from confronting their own mortality. Therefore, results from a three-year NHRI-funded study will be presented and discussed on the following issues: (1) longitudinal changes in prognostic awareness, physician-patient discussions, and LST preferences in terminally ill cancer patients’ dying process; (2) the concordance between terminally ill cancer patients’ states of preferred and actual LSTs over the 6 months before their death; and (3) impact of accurate prognostic awareness on terminally ill cancer patients’ psychological distress and QOL as well as preferences of LSTs. This study was conducted on a convenience sample of 303 terminally ill cancer patients recruited in 2010-2012 from the general medical inpatient units of a medical center in northwest Taiwan and followed through December 2015.

# Use the four-box method to enhance shared decision making for end of life care

## 臨床倫理四主題討論用於末期醫病共享決策討論

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The doctor-patient relationship has changed a lot in recent years. Clinicians may face many difficult ethical issues when encountering patient who suffers late stage disease, such as futile therapy or medical futility, palliative treatment in the end of life,withhold or withdraw of life sustaining treatment, etc. Shared decision making (SDM), defined as: “an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences”, provides a model for patients and clinicians to participate in the communicative process about health care decisions that has no clear best option. The “Four-Box Method”adapts the same core conceptsof SDM but uses a case-based approach to facilitate the decision making. In “medical indication”, the physician proposes the diagnosis or treatment options according to the current available evidence. “Patient preference”highlights what the patient wants and “quality of life” involves the patient’s capacity to enjoy him or herself. Everything else that is not discussed is put into “contextual features”, is put into this box. After all the information been collected in the four boxes, the relationship between these materials and the ethics principles could be evaluated, then the ethics issue could be established and the medical decision could be made through this shared decision process.

# Improve end-of-life care: Start from understanding the status of aggressive care in terminal patients had withdrawal of mechanical ventilation

# 改善生命末期照護：從了解罹患末期疾病撤除呼吸器病人的侵犯性治療開始

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**Background:** For patients who are terminal ill, once the outcome of treatments could not maintain a meaningful life, the treatment goal may transit to a comfort-oriented care. At that time, withdrawal of life-sustaining treatments may be under concerned to lessen patients' suffering. Previous studies reported some aggressive treatments at end-of-life (EOL) care. The aim of this study was to explore aggressive care in terminal patients had withdrawal of mechanical ventilation.

**Methods:** This study was conducted in a tertiary hospital in Taiwan by retrospective chart review. Patients 20 years and older who on hospice shared care for discussing of withdrawal of mechanical ventilation were identified and their medical charts were reviewed. Covariates including age, sex, education level, religious believes, marital status and occupation, medical condition of major diagnosis and comorbidities were recorded. Aggressive EOL care including usage of vasopressors, antibiotics, artificial nutrition with total parenteral nutrition / peripheral parenteral nutrition and tube feeding were recorded. Medications for symptoms relief including opioids and sedatives were also recorded. Statistical analyses were performed by SPSS 20.0.

**Results:** A total of 153 patients who under hospice shared care for discussion of withdrawal of mechanical ventilation were identified during January 2013 and December 2015.The mean age of all patients was 72.9 years (SD=17.0) and 94 (61.4%) were male. The top three diagnoses were terminal lung diseases (n= 70, 45.8%), malignancy (n= 55, 35.9%), and terminal diseases of brain (n= 14, 9.2%). One hundred and eighteen (77.1%) patients had withdrawal of mechanical ventilation. On the day of ventilation withdrawal 48 (40.7%) patients were administering with vasopressors, 71 (60.2%) with antibiotics, and 115 (97.5%) were supported by nutrition while 98 (83.1%) were prescribed with opioids and 73 (61.9%) with sedatives, respectively.

**Conclusion:** Most patients under hospice shared care for discussing mechanical ventilation withdrawal had been withdrawn from the ventilation. However, many of them still received aggressive treatments on the day of withdrawal.

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## 鼻腔鼻竇惡性腫瘤的治療趨勢

# Current Trends in Treating Sinonasal Malignancis

時 間：106年6月10日 13:30~17:00

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地 點：台北國際會議中心 201C 會議室

Place：Conference Room 201C
Taipei International Convention Center

# 鼻腔鼻竇惡性腫瘤的治療趨勢

# Current Trends in Treating Sinonasal Malignancis

# Overview of sinonasal malignancies

# 鼻腔鼻竇癌概論

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Sinonasal malignancies represent a group of malignant tumors arising in nasal cavity and/or its adjacent paranasal sinuses. They constitute around 3% of head and neck cancers and less than 1% of all malignancies. According to World Health Organization, the annual incidences were reported <1.5 per 100,000 in men and <1 per 100,000 in women. Apart from its rarity, sinonasal malignancy comprises a variety of heterogenous tumor histology, and therefore a wide range of disease process and tumor behavior. Squamous cell carcinoma and its variant (verrucous, papillary, basaloid or spindle cell) are the most prevalent histopathologies. Other cell types include lymphoepithelial carcinoma, sinonasal undifferentiated carcinoma, adenocarcinoma, carcinoma derived from salivary glands, neuroendocrine tumor, esthesioneuroblastoma, malignant melanoma, sarcoma, and lymphoma. Beside all these diverse categories, a few newly described neoplasms have also been reported recently, such as NUT midline carcinoma and HPV-related carcinoma with adenoid cystic-like features.

The clinical presentations of sinonasal tumors are usually nonspecific. The symptoms such as nasal obstruction, purulent rhinorrhea and epistaxis are sometimes mistaken for sinusitis. The diagnosis would be delayed until those obscure tumors violate the orbit, the brain, the cranial nerves or the great vessels. Surgical resection remains the mainstay of treatment (except for lymphoma), albeit the proximity to vital structures limits its effectiveness. Adjuvant therapy should be tailored if adequate surgical margins could not be achieved. The treatment outcome and prognosis varied, remarkably depending on the histology type and extent of involvement (i.e. tumor staging). This talk will give an overview of sinonasal malignancies and briefly report the treatment results in Taipei Veterans General Hospital.

# Skull base surgery for sinonasal malignancies

# 鼻腔鼻竇癌的顱底手術

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Sinonasal tumors are rare tumors but with the greatest histologic diversity. Due to its proximity to the skull base, advanced sinonasal malignancy may present with skull base or intracranial involvement. Surgery is the main treatment modality for most sinonasal malignancy, except lymphomas or sinonasal undifferentiated carcinomas. Various surgical approaches have been developed for managing sinonasal tumors, including craniofacial resection, lateral rhinotomy, midfacial degloving, maxillectomy and endoscopic endonasal approach (EEA). For selected advanced cases (without extensive orbit or facial soft tissue involvement), EEA could achieve similar oncologic efficacy with reduced morbidity. Nowadays, EEA has developed to be the most efficient surgical corridor for multiple skull base pathologies. Two surgeons (neurosurgeon and ENT doctor) using a four-handed technique with image guidance is the current trend in treating this kind of complicated disease.

The classification of EEA is mainly divided into two categories, sagittal plane and coronal plane, based on anatomic relationships and orientation in radiologic planes. The sagittal plane extends from the frontal sinus to the second cervical vertebra, while the coronal plane includes three planes corresponding to the anterior, middle, and posterior cranial fossae. Familiar with the anatomy of the sinuses and various skull base structure and proper surgical techniques allow safe dissection in these planes to prevent critical neurovascular injury during the surgery. Meticulous hemostasis and repair of skull base defect with multilayered technique can prevent possible postoperative hemorrhage and cerebrospinal fluid (CSF) leaks.

# Role of radiotherapy in treating sinonasal malignancies

# 放射線治療的在鼻腔鼻竇癌的角色

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Sinonasal tumors are uncommon malignancies, representing about 0.2–1 % of all cancers, with 5-year overall survival rate around 50% and local control rate of 50-70 % in reported series. The disease is characterized by a high heterogeneity both in primary site and histology. The most common histologies include the keratinizing or non-keratinizing squamous cell carcinomas, followed by adenoid-cystic carcinomas and adenocarcinomas, whereas neuroectodermal and neuroendocrine tumors, as well as soft tissue tumors may also occur.

Treatment for sinonasal tumors is challenging because of their proximity to critical structures. Surgical resection is the mainstay of treatment. However, complete resection with organ preservation is often limited due to anatomic characteristics of the head and neck region and the close proximity of the sinonasal lesions to the critical organs, as well as the tumors often infiltrate critical adjacent structures. For unresectable tumors, definitive radiotherapy or chemoradiotherapy is used but the outcomes are suboptimal with significant toxicity because higher radiation doses are needed to control gross tumor. Postoperative radiation therapy is indicated when adverse features are found at the time of surgery. These include advanced T stage, high tumor grade or high-risk histology, perineural invasion, lymphovascular space invasion, positive lymph nodes, positive margins, and surgeon concern about the adequacy of resection.

Because sinonasal tumors have the propensity to present at an advanced stage and the presence of nearby critical structures, such as optic nerve, patients are at risk of severe radiation-induced long-term toxicity. Conventional radiotherapy technique has been reported to be associated with either incomplete target coverage or severe toxicity, such as radiation-induced retinopathy or neuropathy. Recent advances in radiotherapy technique, e.g. intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), particle therapy, have greatly improved therapeutic ratio between tumor control and normal tissue toxicity, but efforts to balance local control with acceptable morbidity may result in marginal and out-of-field failures. Good cooperation between surgeons and radiation oncologists is necessary for optimal patient care.

# The role of chemotherapy and immunotherapy in treating sinonasal malignancies

## 化學治療及免疫治療的在鼻腔鼻竇癌的角色

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Cancers arising from sinonasal cavities are usually considered as a part of head and neck cancers. The major pathologic type of sinonasal malignancies is squamous cell carcinoma (SCC), which is consistent with the pathology of cancers originating from other location of the head and neck region. Regarding the treatment of advanced head and neck SCC (HNSCC) including sinonasal malignancies, chemotherapy, radiotherapy, and anti-epidermal growth factor receptor (EGFR) therapy are the mainstay of treatments. In recent years, a greater understanding of the HNSCC biology promotes the rapid development of immunotherapies. The immune system plays a key role in the development, establishment, and progression of HNSCC. HNSCC cells evade the host immune system through manipulation their immunogenicity, production of immunosuppressive cytokines, and promotion of immunomodulatory cell types. Thereby, immunotherapies of HNSCC aim to target the HNSCC with immunogenicity, to intercept the immunosuppressive cytokines, and to modulate tumor microenvironments by adoptive cell therapies. In recent years, promising results in HNSCC immunotherapies encourage clinicians in treating advanced HNSCC. The major strategies include cancer vaccines, adoptive immune cell therapies, antibodies against the tumor-associated antigens and cytokines, and immune checkpoint blockades. In this presentation, we will summarize the updated information about the role of chemotherapy and immunotherapy in sinonasal malignancies.

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## 醫病共同決策在慢性腎臟病人全人照顧的應用

## Shared Decision Making in Chronic Kidney Disease

時　間：106年6月10日　　13:30~17:30

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Taipei International Convention Center

# 醫病共同決策在慢性腎臟病人全人照顧的應用

# Shared Decision Making in Chronic Kidney Disease

# The new movement of hospice and palliative care in Taiwan

# 台灣安寧緩和醫療新運動

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**Hospice and Palliative Care in Taiwan**

The Ministry of Health and Welfare organized a taskforce to develop hospice and palliative care in 1995. National Health Insurance (NHI) subsidised hospice homecare (starting with cancer in 1996) and an inpatient care system (initiated for cancer in 2000, and motor neuron disease in 2003). Hospice Palliative Care Act was enacted in 2000 and Patient Autonomy Act passed in 2015. Currently, National Health Insurance provide palliative care for inpatient, home care, shared care, and community-based care.

According to the 2015 Quality of Death Index published by the Economist Intelligence Unit, Taiwan ranked 6th in the world and 1st in Asia. Those top ranking countries have comprehensive national policy frameworks for palliative care, integrate palliative and hospice care into healthcare systems, provide well-established training program for healthcare professionals and lay-persons, offer affordable services, prescribe opioid analgesics, and raise the awareness.

**Taiwan New Movements in Hospice and Palliative Care**

Palliative care is no longer offered with preference to cancer patients, but also to patients with non-cancer such as vital organ failure, motor-neuron disease, HIV, the frail elderly, and severe dementia. We will face a growing number of patients dying from non-cancer diseases. Policies focused on enhancing the palliative care not only community-based hospice, but also the development of palliative care in nursing home, ICU, ER and early palliative care for patients with advanced cancer. Furthermore, the advocacy of Advance care planning (ACP), share decision-making (SDM) and patient self-determination will be the new movements in Taiwan.

# Shared decision making in chronic kidney disease: UK experience

## 醫病共同決策在慢性腎臟病人照顧的應用：英國之發展

**Martin Wilkie**

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Shared decision making describes involving patients as equal partners in the decision making process. Patient involvement in health care comes in a variety of forms including engaging people to keep healthy, shared decision making, choosing a provider and self-management support (Kings Fund 2014). Patient training is central to the provision of dialysis home therapies in order to give individuals the required skills to manage their condition in the community away from the hospital. Alternatively those who receive their dialysis treatment at centres are much less likely to be engaged in their own treatment. There is growing evidence that informing patients about their condition and providing educational opportunities for them to engage in their own care leads to improved outcomes.

From 25 years of working within a dialysis home therapies clinic I have learned to value the motivation that people have to remain as independent of the hospital as possible and to take a role in managing their own care. Key to this is the role of the health care professional – which should be to support independence where possible, rather than disabling patients by doing everything for them. In my talk, I will review evidence around the use of decision aids to support dialysis modality choice including the Yorkshire Dialysis Decision Aid as the development of Shared Haemodialysis Care in which people who receive their dialysis at centres are supported to learn aspects of their own care.

# Shared decision making in chronic kidney disease: Taiwan experience

# 醫病共同決策在慢性腎臟病人照顧的應用：台灣之發展

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Hemodialysis (HD) and peritoneal dialysis (PD) have similar outcomes, with differences only for specific subgroups. However, few patients have the necessary knowledge to understand well the difference between these two dialysis modalities. Besides, patients' opinions were not always fully considered in the choice of dialysis modality in ESRD patients, and most patients depend on physicians' opinions to determine dialysis modality.

Recently, patient-centered outcomes and quality of life for patients with kidney disease have been emphasized. In clinical practice, modality choice should be individualized, with the aim of maximizing quality of life, patient-reported outcomes and achieving patient-centered goals. It's difficult for patients to under the complex knowledge of dialysis. A well-structured decision aid is necessary to help patients to reveal their preference for treatment.

By a shared decision-making (SDM) program, we helped patients in chronic kidney disease stage 5 to choose a dialysis modality which has least negative impact on their life quality or can fulfill the wish of lifestyle after initiating dialysis. The SDM program includes a 30-minute interactive flash software, highlighting the difference between HD and PD, and requiring patients to fill in their choice or data. Patients will always be accompanied by experienced PD nurse when they operate the interactive software.

We also analyzed factors affecting patients' modality choice. Factors favoring PD are 1) strong self-care will, 2) a high degree of family support/help, 3) hoping to do dialysis in your home, and 4) wishing to keep as much independence as possible. Factors favoring HD are 1) fear of complications of PD, and 2) feeling safer to go to a medical place to have dialysis done. Age was not an independent determinant of dialysis modality.

# Shared decision making in hospice and palliative care of end-of-life renal patients

## 醫病共同決策在生命末期腎病患者安寧緩和醫療的應用

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Shared decision-making (SDM) is a process integral to clinical practice, one where the healthcare provider/professional and the patient discuss treatment alternatives based on patient values and life circumstances and make a decision about whether and how to proceed with treatment. The Legislative Yuan enacted the Patient Self-Determination Act (PSDA) on December 18, 2015 and promulgated three years after its announcement. According to PSDA, patients have the right to express their wishes to stop treatment by advance decision/directive (AD) via advance care planning (ACP), provided by approved medical institutions. Before the patient's wished are acted upon, two physicians specialized in fields related to the patient's illness will do a survey first in five clinical situations, including being terminally ill, in a coma or persistent vegetative state, with advanced dementia or incurable diseases, an intolerable condition without any other treatment option. Then the palliative care team must confirm the person's condition twice. The concepts of SDM could be consolidated in the palliative care family conference during ACP discussion and documentation of AD.

For end-of-life renal patients and renal supportive care (RSC) team, SDM is an effective model for discussing issues of proceeding or forgoing dialysis, or even hospice-palliative care. The tools for short-term prognosis prediction can also be applied for renal frail phenotype identification. This lecture arguments that nephrologists and RSC team possess the professional knowledge and basic skills to provide decisional coaching and to implement SDM in primary care settings. Of particular importance are the values that balance professionalism in daily practice, and respect patient self-determination, which is the basis of SDM, and the ability to maintain neutrality.

# 「醫學研究論文獎」及
# 「盧致德獎」論文摘要

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

# 「醫學研究論文獎」及「盧致德獎」論文摘要

1. 財團法人中華醫學研究獎助基金會
   Etiologies and outcome of osteonecrosis of the femoral head: Etiology and outcome study in a Taiwan population ..... Shang-Wen Tsai

2. 財團法人消化醫學研究發展基金會
   N-Acetyltransferase 2 (NAT2) genetic variation and the susceptibility to noncardiac gastric adenocarcinoma in Taiwan..... Chih-Hao Chang

3. 財團法人兼善醫學基金會
   Adjuvant chemotherapy with tegafur/uracil for more than 1 year improves disease-free survival for low-risk Stage II colon cancer..... Je-Ming Hu

4. 財團法人心臟醫學研究發展基金會
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# Etiologies and outcome of osteonecrosis of the femoral head: Etiology and outcome study in a Taiwan population

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## ABSTRACT

**Background.** Osteonecrosis of the femoral head (ONFH) is an important indication for total hip arthroplasty in Taiwan. We demonstrated the etiologies of ONFH and outcomes based on stratification of patients according to different etiologies.

**Methods.** We reviewed medical records and images from January 2000 to May 2010 in our database with the diagnosis of "osteonecrosis of the femoral head." We categorized all patients into different etiologies, including corticosteroid, alcohol, and idiopathic. All patients received subsequent follow up for ipsilateral precollapse ONFH and contralateral disease-free femoral head status after initial diagnosis.

**Results.** Of the 1153 patients who had undergone 1674 hip surgeries including core decompression and total hip replacement, alcohol use was the most prevalent etiology in our population (45.2%). Patients with corticosteroid- and alcohol-associated ONFH were younger and more likely to have bilateral disease. Patients with alcohol- or steroid-associated ONFH were found to have a higher rate of contralateral disease and faster progression of precollapse ONFH than patients who had or had not undergone core decompression.

**Conclusion.** Alcohol use had the greatest impact on ONFH in our population. Nonidiopathic ONFH patients had the worst outcome. Understanding the nature of progression of ONFH and incidence of contralateral disease may provide great prognostic value to detect and perform early intervention.

**Keywords.** avascular necrosis; etiology; femoral head; osteonecrosis; outcome

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# N-Acetyltransferase 2 (NAT2) genetic variation and the susceptibility to noncardiac gastric adenocarcinoma in Taiwan

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**ABSTRACT**

**Background.** N-Acetyltransferase (NAT) is an important enzyme with the capacity to metabolize carcinogenic aromatic amines. However, it remains controversial whether the encoded functional NAT2 genetic polymorphism is related to the risk of gastric adenocarcinoma (GA). The aim of this study was to evaluate the association between NAT2 genetic variation and gastric adenocarcinoma (GA), with special reference to the gastric noncardiac adenocarcinoma (GNA).

**Methods.** Peripheral white blood cell DNA from 368 GA patients and 368 age- and sex-matched controls were genotyped for NAT2 by a polymerase chain reaction method. The lifestyle habits of the participants were assessed using a semiquantitative food-frequency questionnaire. NAT2 genotype, interaction with lifestyle habits, and the risk of GA and GNA were analyzed by logistic regression.

**Results.** GA patients were more likely to have a smoking habit, ate more salted foods, and consumed more well-done meat than the controls. There was no association between the NAT2 genotypes and susceptibility to GA. However, if patients with gastric cardiac adenocarcinoma (GCA; n = 42) were excluded, the NAT2 slow acetylators (without rapid acetylator allele) had a higher risk of GA than intermediate and rapid acetylators (odds ratio = 1.53; 95% confidence interval, 1.05–2.23, $p$ =0.027). In addition, there was a synergic effect of NAT2 slow acetylator and well-done meat intake to the development of GNA (odds ratio = 3.83; 95% confidence interval, 1.68–8.76, $p$ = 0.001).

**Conclusion.** NAT2 slow acetylators have a higher risk of GNA than intermediate and rapid acetylators have in a Taiwanese population. The intake of well-done meat, an additive to the acetylator status, may contribute to the incidence of gastric carcinogenesis.

**Keywords.** arylamine N-acetyltransferase; gastric adenocarcinoma; gastric cancer; stomach neoplasms

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# Adjuvant chemotherapy with tegafur/uracil for more than 1 year improves disease-free survival for low-risk Stage II colon cancer

**Je-Ming Hu [a], Yu-Ching Chou [b], Chang-Chieh Wu [a], Cheng-Wen Hsiao [a], Chia-Cheng Lee [a], Chun-Ting Chen [c], Sheng-I Hu [a], Wei-Tin Liu [a], Shu-Wen Jao [a],***

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**ABSTRACT**

**Background.** It is uncertain whether adjuvant chemotherapy (CMT) improves survival in patients with low-risk Stage II colon cancer. We aimed to determine the disease-free survival (DFS) and 5-year overall survival (OS) of low-risk Stage II colon cancer patients treated with adjuvant tegafur/uracil (UFUR).

**Methods.** From January 2004 to December 2011, the follow-up status of 278 low-risk Stage II colon cancer patients who underwent surgery in a single medical center was retrospectively analyzed. These patients were divided into three groups based on whether they received adjuvant CMT with UFUR, adjuvant CMT with 5-fluorouracil, or surgery alone. DFS and 5-year OS curves were calculated using Kaplane-Meier survival analysis and Cox proportional hazards regression.

**Results.** In the study population, including 278 low-risk Stage II colon cancer patients with a mean age of 68.28 ± 13.01 years, 132 (47.5%) received adjuvant CMTwith UFUR, 49 (17.6%) received adjuvant CMTwith 5-fluorouracil, and 97 (34.9%) underwent radical surgery alone. At 5 years, the adjusted DFS and OS of low-risk Stage II colon cancer patients were 85.5% and 81.8%, respectively, in the surgery alone group and 97.9% and 96.2%, respectively, in the surgery plus UFUR > 12 months group ( $p$= 0.004 and $p$= 0.098, respectively). In multivariate analysis, CMT with UFUR for more than 12 months increased DFS over surgery alone. There was no statistical difference in the 5-year OS.

**Conclusion.** Adjuvant CMT treatment of low-risk Stage II colon cancer patients with UFUR for more than 12 months following surgery improves DFS over surgery alone.

**Keywords.** adjuvant chemotherapy; disease-free survival; low-risk Stage II colon cancer; overall survival; tegafur/uracil

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# Prediction of vascular dementia and Alzheimer's disease in patients with atrial fibrillation or atrial flutter using $CHADS_2$ score

**Ruey-Hsing Chou [a,b], Chun-Chih Chiu [a,b], Chin-Chou Huang [a,b,c], Wan-Leong Chan [a,d], Po-Hsun Huang [a,b,e], Yu-Chun Chen [f,g], Tzeng-Ji Chen [f,h], Chia-Min Chung [i], Shing-Jong Lin [a,b,c,e], Jaw-Wen Chen [a,b,c,j], Hsin-Bang Leu [a,b,d,e,*]**

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## ABSTRACT

**Background.** Atrial fibrillation (AF) is associated with an increased risk of dementia. However, limited data are available on the predictors of dementia in patients with AF. This study aimed to evaluate whether the $CHADS_2$ score could be a useful tool for risk stratification with regard to dementia occurrence among patients with AF.

**Methods.** AF patients were identified from the National Health Insurance sampling database, which has accumulated a total of 1,000,000 participants since 2000. After excluding patients diagnosed with dementia prior to the index day of enrollment, $CHADS_2$ score was measured to investigate its association with the occurrence of dementia, including vascular dementia and Alzheimer's disease.

**Results.** During the mean follow-up period of 3.71 ± 2.78 years, 1135 dementia cases (7.36%) were identified, including 241 cases of vascular dementia and 894 cases of Alzheimer's disease. In multivariate analysis, an increase of 1 point in the $CHADS_2$ score was independently associated with a 54% increase in the risk of vascular dementia (hazard ratio = 1.54; 95% confidence interval, 1.41–1.69; $p < 0.001$) and a 40% increase in Alzheimer's disease (hazard ratio = 1.40; 95% confidence interval, 1.34–1.46; $p < 0.001$).

**Conclusion.** $CHADS_2$ score is a useful predictor for the development of vascular dementia as well as Alzheimer's disease in patients with AF.

**Keywords.** Alzheimer's disease; atrial fibrillation; $CHADS_2$ score; dementia; stroke

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# Concomitant transrectal ultrasound-guided biopsy and transurethral resection of prostate in patients with urinary retention and elevated serum prostate-specific antigen levels

**Ti-Yuan Yang [a,b], Yung-Chiong Chow [a,b,*], Wun-Rong Lin [a,b], Ming-Chung Ko [c], Marcelo Chen [a,b], Huang-Kuang Chang [a,b], Jong-Ming Hsu [a,b], Stone Yang [a,b], Wen-Chou Lin [a,b], Allen W. Chiu [a,b,d]**

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**ABSTRACT**

**Background.** There was no consensus about the management of patients with urinary retention and elevated serum prostate-specific antigen (PSA) levels. This study aimed to determine whether concomitant transrectal ultrasound (TRUS)-guided biopsy and transurethral resection of prostate (TURP) is practical in patients with urinary retention and elevated serum PSA levels.

**Methods.** From March 2007 to May 2015, a total of 34 patients with urinary retention and elevated PSA ( $\geq$ 4 ng/mL) underwent concomitant TRUS-guided biopsy and TURP. The medical records were evaluated retrospectively, and data including PSA, prostate volume, TURP results, TRUS-guided biopsy results, length of hospitalization, and complications were collected. These patients were then compared with 40 patients with urinary retention who underwent TURP alone.

**Results.** The mean age of the patients was 71.6 years. The mean PSA levels were 16.9 ng/mL. Prostate cancer was detected in eight cases (23.5%): one case by TRUS-guided biopsy alone, two cases by TURP alone, and five cases by both TRUS-guided biopsy and TURP. Complications included fever in five patients (14.7%), recatheterization for urine retention in two patients (5.9%), urinary tract infection in two patients (5.9%), *and de novo* urge incontinence in seven patients (20.6%). The complication rate was not significantly increased compared with that of the patients who underwent TURP alone.

**Conclusion.** This study showed that concomitant TRUS-guided biopsy and TURP was safe and of possible clinical significance in urinary retention patients with elevated serum PSA.

**Keywords.** prostate cancer; prostate-specific antigen; transrectal ultrasound-guided biopsy; transurethral resection of prostate; urinary retention

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# Effects of total saponins from Rhizoma Dioscoreae Nipponicae on expression of vascular endothelial growth factor and angiopoietin-2 and Tie-2 receptors in the synovium of rats with rheumatoid arthritis

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**ABSTRACT**

**Background.** This study aimed to determine the effects of total saponins from Rhizoma Dioscoreae Nipponicae (TS-RDN) on the expression of vascular endothelial growth factor (VEGF) and angiopoietin (Ang)-2 and Tie-2 (endothelial tyrosine kinase receptor) receptors in the synovium of rats with rheumatoid arthritis (RA) (collagen-induced arthritis; CIA), and to examine the mechanisms of TS-RDN in alleviating RA.

**Methods.** The CIA rat model was established and the animals were randomly divided into control, CIA model, TS-RDN, diosgenin, and tripterygium groups. Fluorescent polymerase chain reaction was performed to detect VEGF expression in the rat knee joint synovium. Additionally, immunohistochemical assay was used to detect protein expression of Ang-2 and Tie-2 in the rat knee joint synovium.

**Results.** Expression of VEGF, Ang-2, and Tie-2 in the model group was significantly higher than in the control group ( $p < 0.01$). After TS-RDN, tripterygium and diosgenin treatment, VEGF and Ang-2 expression was lower than in the model group ( $p < 0.01$). However, Tie-2 expression showed no significant difference. The effects of TS-RDN on VEGF expression were more marked than those of tripterygium and diosgenin ( $p < 0.01$).

**Conclusion.** TS-RDN might reduce the expression of VEGF, Ang-2, and Tie-2 in the synovium, thus inhibiting synovial angiogenesis and playing a therapeutic role in RA.

**Keywords.** angiogenesis; angiopoietin 2; Rhizoma Dioscoreae Nipponicae; Tie-2; total saponins; vascular endothelial growth factor

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# Efficacy of continuous theta burst stimulation of the primary motor cortex in reducing migraine frequency: A preliminary open-label study

**Pei-Ru Chen [a,c], Kuan-Lin Lai [a,b,c,d], Jong-Ling Fuh [a,c], Shih-Pin Chen [a,c], Pei-Ning Wang [a,c], Kwong-Kum Liao [a,c], Shuu-Jiun Wang [a,c,e,*]**

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**ABSTRACT**

**Background.** Theta burst stimulation is a type of pattern-specific repetitive transcranial magnetic stimulation that requires less stimulation time and lower intensity to induce long-lasting effects comparable to those of other repetitive transcranial magnetic stimulation protocols. This pilot study investigated whether continuous theta burst stimulation (cTBS) on the primary motor cortex reduced headache frequency in patients with migraine.

**Methods.** Nine patients with migraine were recruited into our study. All patients received 20 cTBS sessions (bursts of 3 50-Hz TMS pulses at 200-ms intervals for 40 seconds), administered every weekday for 4 consecutive weeks. All patients kept headache diaries for 4 weeks before stimulation (baseline; T1), during stimulation (T2), and 4 weeks after stimulation (T3). The primary outcome measures were the changes of total headache and migraine days from baseline (Wilcoxon signed-rank test; T2 and T3 vs. T1).

**Results.** The number of total headache days was reduced at T2 and T3 compared with T1 [9.4 ± 6.2 days ( $p$= 0.024) and 8.7 ± 10.1 days ( $p$= 0.012) vs. 13.4 ± 10.1 days]. The number of migraine days was also reduced at T2 and T3 compared with T1 [2.9 ± 2.7 days ( $p$= 0.021) and 1.0 ± 1.6 days ( $p$= 0.008) vs. 8.6 ± 8.7 days].

**Conclusion.** Our results indicate that cTBS on the primary motor cortex might reduce the number of total headache and migraine days in patients with migraine. However, large-scale randomized controlled trials are necessary to further validate the findings.

**Keywords.** continuous theta burst stimulation; primary motor cortex; repetitive transcranial magnetic stimulation

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# Adjust cut-off values of immunohistochemistry models to predict risk of distant recurrence in invasive breast carcinoma patients

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## ABSTRACT

**Background.** Multigene assays are recommended for hormone receptor-positive invasive breast carcinoma to determine the risk of recurrence, but they are highly expensive. We investigated the prognostic values of immunohistochemistry (IHC)-based prognostic models as an alternative to multigene assays.

**Methods.** The risk categories estimated by the IHC-based prognostic models were correlated to those estimated by the multigene assays in 71 cases and the follow-up results in 642 consecutive cases of HER–2 luminal-type early breast cancer. Cut-off values of IHC-based models were adjusted based on survival outcome to reveal maximum Harrell C index or based on the maximum positive likelihood ratio correlated to multigene assay.

**Results.** All investigated IHC-based models could predict the risk of distant recurrence, but their cut-off values required adjustment. Using distant recurrence-free survival (DRFS) to refine the cut-off values could improve the prognostic values. Adjusting the cut-off values using the results of multigene assays, the positive predictive values of an estimate of low risk or low recurrence score ( $\leq 21$) were higher than 90%. On average, 23% of cases got different results of risk assessment after adjustment. Although cut-off values adjusted by multigene assay were not identical to those refined by survival, the adjusted values (17.1 and 23.8) and the refined values (17.5 and 24.5) of the best model (Magee Eq. 1) were close. Among all the evaluated models, Magee equation 2 was the only one without Ki67, and its prognostic values were the lowest. Using 20% as cut-off for Ki67 as suggested by St. Gallen consensus, we could confidently define luminal A cancer.

**Conclusion.** It is necessary to adjust the cut-off values of IHC-based prognostic models to fit the purpose. If the estimated risk is clearly high or low, it may be reasonable to omit multigene assays when cost is a consideration.

**Keywords.** breast neoplasms; gene expression profiling; immunohistochemistry; prognosis

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# Screening for Anti-lipase Properties of 37 Traditional Chinese Medicinal Herbs

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**ABSTRACT**

**Background.** To find new, crude anti-obesity drugs from natural sources through the inhibition of adsorption of dietary lipids, *in vitro* porcine pancreatic lipase (PPL; triacylglycerol lipase, EC 3.1.1.3) inhibitory tests were carried out on selected plants with weight-reducing or related potential, used in Chinese traditional medicine.

**Methods.** The methanolic extracts of 37 traditional Chinese herbal medicines of different families were assayed for their *in vitro* activity against PPL by using spectrophotometry with 2,4-dinitrophenyl butyrate as a synthetic substrate. Coexistent phytochemicals, or those present in high levels, in the 3 most promising Chinese herbs were tested for their anti-lipase activity.

**Results.** Extracts from 2 herbs, *Prunella vulgaris* L. (Labiatae) and *Rheum palmatum* L. (Polygonaceae), at a concentration of 200 μg/mL, significantly inhibited PPL—by 74.7% and 53.8%, respectively. Quercetin exhibited better activity (27.4%) than all the other phytochemicals at a final concentration of 25 μg/mL in the assay system, followed by luteolin, with an activity of 17.3%.

**Conclusion.** The results support the view that herbs represent a rich source of anti-lipase compounds. The screening of the methanolic extracts of 37 Chinese medicinal plants *in vitro* led to the identification of several extracts with potential activity against PPL, in particular, *P. vulgaris* and R. *palmatum*. We also found that several monomeric chemicals in these herbs exhibited good or moderate activity against PPL. To the best of our knowledge, these traditional Chinese herbal medicines or phytochemicals have not been previously screened for their lipase inhibitory activity.

**Keywords.** anti-lipase activity, anti-obesity agents, Chinese herbal drugs, *Prunella vulgaris* L., *Rheum palmatum* L.

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  中、重度腎功能不全(腎絲球濾過率分別為30-59及15-29mL/min/1.73m²)及正接受血液透析的末期腎臟病：起始量為每日一次1mg，最高劑量為每日一次2mg。
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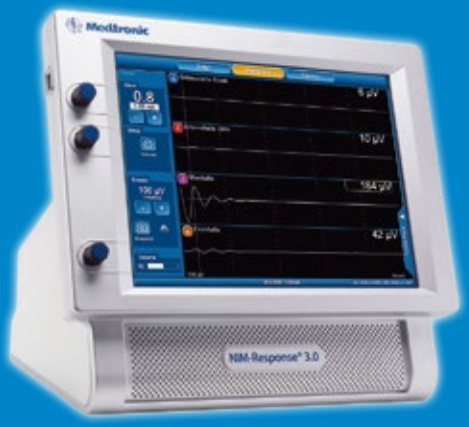


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