



臺中榮民總醫院  
Taichung Veterans General Hospital

臺中榮民總醫院一一〇年度與中區各大學院校合作研究計畫

# 110年度 臺中榮民總醫院與中區各大學院校 合作研究計畫

聯合成果發表會



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國立暨南國際大學、靜宜大學、國立聯合大學

# 110 年度臺中榮民總醫院 與中區各大學院校 合作研究計畫

主辦單位 臺中榮民總醫院

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逢甲大學、國立臺中科技大學、國立暨南國際大學、  
靜宜大學、國立聯合大學  
(依單位筆劃序)

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# 110 年度

## 臺中榮民總醫院與中區各大學院校合作研究計畫 聯合成果發表會

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### 主辦單位

臺中榮民總醫院

### 協辦單位

大葉大學、中臺科技大學、國立中興大學、弘光科技大學、東海大學、南開科技大學、逢甲大學、國立臺中科技大學、國立暨南國際大學、靜宜大學、國立聯合大學(依單位筆劃序)

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許碧紋

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<u>靜宜大學</u>	林智健 (研發長)		吳曉華		
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TCVGH-HK1108001

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臺中榮民總醫院/研究助理  
弘光科技大學/碩士

# 榮東計畫

TCVGH-T1107801

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蔡耀德  
劉士嘉  
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東海大學工業工程與經營資訊學系/專任助理  
東海大學工業工程與經營資訊學系/碩士生

TCVGH-T1107802

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P26

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TCVGH-T1107803

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TCVGH- T1107804

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P29

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TCVGH-T1107805

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TCVGH-T1107806

以弱監督深度學習為基礎之白斑症治療評估系統建置

P33

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TCVGH-T1107807

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TCVGH-T1107808

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**TCVGH-T1107809**

**透過服務設計改善住院兒童復原力、希望與期望之研究—以 VR 體驗為例**

**P37**

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**TCVGH-T1107810**

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**P39**

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臺中榮民總醫院心臟血管中心/放射師

**TCVGH-T1107811**

**探討合成胜肽之抗異位性皮膚炎功效 (II)**

**P40**

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臺中榮民總醫院藥劑部/科主任  
東海大學化學系/博士生

## 榮科計畫

TCVGH-NTCNC1108501

人工智慧應用於護理人員於執業環境之壓力分析：  
以台中榮民總醫院外科病房為例

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陳大仁  
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陳筱瑤  
李雅婷  
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國立臺中科技大學  
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國立臺中科技大學  
國立臺中科技大學  
國立臺中科技大學

TCVGH-NTCNC1108502

人工智慧協助子宮內膜切片診斷

P44

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東海大學/工程師

## 榮逢計畫

- TCVGH-FCU1108201**      **利用小波包轉換與自適應共振理論於動靜脈瘻管狹窄程度分類之研究**      **P46**
- 邱創乾      逢甲大學自動控制工程學系/教授  
陳呈旭      臺中榮總內科部腎臟科/主任醫師  
周怡華      臺中榮總腎臟科/護理師  
林瑜成      逢甲大學自動控制工程學系/學生  
李政修      逢甲大學自動控制工程學系/學生
- TCVGH-FCU1108202**      **應用深度學習於新生兒膽道閉鎖之超音波影像辨識**      **P48**
- 許芳榮      逢甲大學資訊工程系/教授  
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黃聖揚      臺中榮民總醫院兒童外科/主治醫師  
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王佳瑀      逢甲大學資訊工程系/碩士生  
范藝齡      逢甲大學資訊工程系/碩士生
- TCVGH-FCU1108203**      **人工智慧技術用於麻醉前辨別異常呼吸音監測系統**      **P50**
- 蔡鈺鼎      逢甲大學精密系統設計學士學位學程/副教授  
林明志      臺中榮民總醫院兒童醫學中心/主任  
沈靜慧      臺中榮民總醫院麻醉部/主任  
劉宇瑄      逢甲大學電聲學程/研究生  
李旻軒      逢甲大學電聲學程/研究生
- TCVGH-FCU1108204**      **以機器學習實現糖尿病住院患者的精準血糖值與再住院預測**      **P52**
- 林英志      逢甲大學應用數學系/副教授  
潘錫光      臺中榮民總醫院胃腸科/主治醫師  
沈宜靜      臺中榮民總醫院新陳代謝科/主治醫師  
張誌翰/簡慈瑩/魏昶泰/張維展      逢甲大學應用數學系/兼任助理

TCVGH- FCU1108205

以深度學習實現以最少生理訊號識別睡眠呼吸中  
止症類型之研究

**P53**

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# 榮開計畫

<b>TCVGH-NK1109001</b>	<b>開刀房護理人員排班系統(IV)</b>	<b>P55</b>
林志鴻 蔣鋒帆 吳叔如	南開科技大學餐飲管理系 臺中榮總重症醫學部 臺中榮總護理部	
<b>TCVGH-NK1109002</b>	<b>決定UV LED陣列系統的殺菌條件</b>	<b>P56</b>
紀璟睿 毛彥喬	南開科技大學餐飲管理系 臺中榮民總醫院急診部	
<b>TCVGH-NK1109003</b>	<b>UV LED 小型陣列系統之立體弧度角功率之分析</b>	<b>P58</b>
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<b>TCVGH-NK1109004</b>	<b>開發以計畫AIoT為基礎的大數據蒐集系統</b>	<b>P59</b>
陳百薰 賴國隆 劉伯瑜 林志鴻	南開科技大學多媒體動畫應用系 臺中榮民總醫院過敏免疫風濕科 臺中榮民總醫院感染科 南開科技大學餐飲管理系	

## 榮葉計畫

### TCVGH- DYU1108301

不同基因亞型乳癌存活者之復發狀態、創傷後成長、照護需求及生活品質：病歷回溯暨橫斷性研究

P60

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大葉大學/學士班學生

### TCVGH-DYU1108302

探討台灣本土大蟬花Wu-BFP-14的生物安全性與保護肝臟功效機制

P62

蔡明勳  
鄒錫凱  
符羽嘉  
來品言

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中山醫學大學生物醫學科學系研究所/碩士生  
中山醫學大學生物醫學科學系/大學生

### TCVGH- DYU1108303

探討蛹蟲草和蟬花應用於蟑螂過敏原誘發異位型皮膚炎細胞模式之治療機轉

P64

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大葉大學生科中心/教授  
臺中榮總研究部/副研究員

## 榮譽計畫

### TCVGH-NCNU1107901

內分泌訊息調節嗅覺感覺神經元的突觸發生與功能並影響雄果蠅同性間求偶行為的發生

P65

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### TCVGH-NCNU1107902

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**TCVGH-PU1108105**

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## 榮聯計畫

TCVGH-NUU1108901

利用深度學習方法，開發異常心肺音區段偵測與辨識系統

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# 成果報告摘要

**比較結核與非結核分枝桿菌病患於生活品質與身體意象之差異-混合研究**

Comparing differences in quality of life and body image between tuberculosis and non-tuberculous mycobacteria patients- A mixed methods study

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**背景：**非結核分枝桿菌(Non-tuberculous mycobacteria, NTM)感染病患的治療療程需持續18-24個月，治療副作用大且易復發，而多數病患的臨床表徵顯非特异性導致診斷延遲，故了解其罹病的經驗顯得重要。

**目的：**探討結核與NTM病患於生活品質與身體意象的情形，及NTM感染病患的疾病經驗。

**方法：**本研究採質量性混合研究設計，本文呈現第一階段的研究結果。第一階段以質性研究法，於中部某醫學中心，以半結構深度訪談收集資料，訪談內容錄音後轉為逐字稿，以內容分析進行主題歸納；第二階段以結構式問卷進行資料收集。

**結果：**共有20位NTM病患參與質性訪談，其疾病經驗呈現四個主題：一、面對疾病混沌不明：1.症狀多樣難以診斷、2.求診過程波折不斷、3.經歷心情高低轉折；二、確定診斷之複雜思緒：1.放下心仍擔憂傳染他人、2.難擺脫疾病標籤化的陰影、3.採利己利他以穩定心情；三、承受疾病治療之苦：1.無奈面對治療之戰、2.承受藥物副作用之苦、3.疾病復發之不確定；四、學習與疾病共存：1.採宿命論詮釋病因、2.強化保護力與增強免疫力、3.被支持的力量。

**結論：**本研究結果可做為日後醫護人員在照護NTM感染病患的參考，以傾聽、提供資訊，強化病患信心以面對漫長治療的苦痛及社會烙印。

**關鍵詞：**非結核分枝桿菌、感染、疾病經驗、質性研究

Background: The clinical presentation for patients with most Non-tuberculous mycobacteria (NTM) infections is non-specific and often results in delayed diagnosis. NTM treatment often lasts 18–24 months and consists of three or more antibiotics that can have serious side effects. Relapses are common and require resumption of prolonged antimicrobial therapy. It is really important to understand the experiences of patients with NTM disease.

Purposes: To explore the quality of life and body image of tuberculosis and NTM patients, and the illness experiences of NTM-infected patients.

Methods: This mixed-methods study combined qualitative and quantitative approaches, and this paper presents the results of the first phase of the study. In the first stage, a qualitative research method was used to collect data through semi-structured in-depth interviews at a



medical center in central Taiwan. The interviews were recorded and converted into verbatim transcripts, and the content analysis was used to summarize the themes; in the second stage, structured questionnaires were used to collect data.

**Results:** A total of 20 NTM patients participated in the qualitative interviews, and their illness experience presented in four themes. The first theme (facing the obscure of NTM) included three subthemes: 1. diverse symptoms are difficult to diagnose; 2. seeking a doctor with twists and turns in the process; 3. going through mood swings; The second theme (determining the diagnosis of complex thoughts) included three subthemes: 1. put down your heart and still worry about transmission to others; 2. It's difficult to get rid of the shadow of disease labeling; 3. self-interest and altruism to stabilize the mood; The third theme (suffering from the pain of disease treatment) included three subthemes: 1. facing helpless the battle of treatment; 2. suffering from drug side effects; 3. uncertainty about disease relapse; The fourth theme (learning and being with disease) included three subthemes: 1. adopting fatalism to explain the cause of disease; 2. strengthen protection and enhance immunity; 3. being supported forces.

**Conclusions:** The results of this study can be used as a reference for medical staff when taking care of patients with NTM infection in the future. Our study also provides relevant information, and strengthen patients' confidence to face the pain and social stigma of long-term treatment in such population.

**Keywords:** Non-tuberculous mycobacteria (NTM), infection, illness experience, qualitative research

## 榮東計畫

**TCVGH-T1107801**

### 醫院勤務效益改善之決策模擬系統

Decision simulation system for improving hospital runner dispatch efficiency

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近年來，台灣對於醫療服務的需求逐年漸增，在醫院資源有限的情況下，需要高效且科學的方式進行資源配置。本計畫以系統模擬技術，就醫院勤務服務流程，結合勤務派工系統資訊，了解目前勤務的分佈與動態，協助醫院建立勤務高效能決策支援系統，以達醫院資源優化之效能。研究結果顯示，智慧派工機制可以降低勤務案件的延誤率，然而也受到諸多的因素影響，故建議後續應該建立更完整的派工機制，並延伸改善醫院勤務服務流程的功能，以提供醫院管理者勤務效率提升之最佳方案。

**關鍵詞：**系統模擬、決策支援系統、醫院勤務

Medical services in Taiwan has been increasing year by year for decades. Therefore, hospitals have to allocate limited resources efficiently in a scientific manner. The proposal aims to develop a decision support system to optimize runner dispatch tasks and other medical resources. A system simulation approach is used to simulate the runner service flow of the hospital. Results of this study show that the smart dispatch mechanism can reduce the delay rate of delivery service. However, the effect of the smart dispatch mechanism may be affected due to the runner service status and routes. Therefore, it is suggested that a more complete dispatch mechanism should be established in the future, and the functions of improving the hospital service process should be extended to provide hospital management. The result can provide the best case of staffing and dispatch.

**Keywords:** system simulation, decision support system, Runner Workforce

**結合認知功能、實體環境、社群關係之整合性失智症檢測及照顧系統**

An Integrated Dementia Test Scale and Care System for Cognitive Function, Physical Environment, and Community Relationship

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隨著失智人口日漸攀升，失智症患者的照顧問題已成為世界性關注的議題。近年許多研究者、專家學者探討失智症的發生原因、藥物及非藥物的治療方式與建立對失智症患者友善的環境來減緩其病程的發展，也開始關注環境、活動方面的規劃設計，希望能給予失智症患者擁有安全適宜的照護環境。另外隨著人們生活水平的不斷上升，我們對環境和居住的品質要求也不斷提升，當然包括失智症患者的照顧和安養護機構。是故本研究致力於探討失智症患者與周圍環境之間的相互作用。我們正整理文獻後，決定修訂 Fleming 開發的「環境監管工具(Environmental Audit Tool, EAT)」，發展符合台灣失智日照中心之照護環境評估量表，融入多項元素用以檢視台灣失智日照中心的照護環境品質。

本研究以文獻回顧法、專家訪談法、實地考察法，再結合老人周全性評估(CGA)和中文版柯恩-曼斯菲爾德躁動量表(Cohen-Mansfield Agitation Inventory, CMAI)作為修訂依據，並參照個案-台灣中部某日間照顧中心的現況，將環境監管工具(EAT)進行修訂。

**關鍵詞：**失智症、認知功能、環境心理學、老人周全性評估、環境監管工具

With the increasing number of people with dementia, the care of people with dementia has become a worldwide concern. In recent years, many researchers, experts and scholars have discussed the causes of dementia, drug and non-drug treatment methods, and the establishment of a friendly environment for dementia patients to slow down the development of the disease. They have also begun to pay attention to the planning and design of the environment and activities. We hope to provide dementia patients with a safe and appropriate care environment. In addition, with the continuous improvement of people's living standards, our requirements for the environment and the quality of living are also constantly improving, including, of course, the care and maintenance institutions for patients with dementia. Therefore, this study aims to explore the interaction between people with dementia and their surrounding environment. After sorting out the literature, we decided to revise the "Environmental Audit Tool (EAT)" developed by Fleming to develop a care environment assessment scale in line with the Taiwan Dementia Sunshine Center, incorporating multiple elements to examine the Taiwan Dementia Sunshine Center's performance. Environmental quality of care.

This study was revised based on literature review, expert interviews, and field visits, combined with Comprehensive Geriatric Assessment (CGA) and Chinese version of the

Cohen-Mansfield Agitation Inventory (CMAI). Revise the Environmental Audit Tool (EAT) with reference to the current situation of a day care center in central Taiwan.

**Keywords:** Dementia, Cognitive Function, Environmental Psychology, Comprehensive Geriatric Assessment, Environmental Audit Tool

**使用機器學習於武漢肺炎案例分析與預測結合社群資訊與空氣品質資料之研究**

A Study on COVID-19 Cases Analysis and Prediction with Social information and Air Quality Data Using Machine Learning

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COVID-19 大流行提高了人們對傳染病傳播的致命程度如何影響許多部門的認識，包括經濟，政治，文化和社會影響。在世界範圍內，快速識別風險因素的 策略也有助於製定公共衛生指南和直接資源。但是，由於分析和預測仍然是一個事件，因此具有挑戰性。在本文中，我們提出了使用社交訊息和空氣品質數據透過機器學習對 COVID-19 病例進行分析和預測的研究。首先，我們將討論 報告的 COVID-19 病例的探索性數據分析。其次，我們將比較幾種預測方法，例如統計和神經網路。我們還發現了其他因子與 COVID-19 的關係，例如社交 媒體訊息，COVID-19 測試，一些世界指數因素和空氣污染物。

**關鍵字：**COVID-19，分析預測，疾病監測，公共衛生，機器學習

COVID-19 pandemic raises awareness of how fatal the spreading of infectious disease impacts many sectors, including economics, political, cultural, and social implications. Across the world, strategies to quickly recognize risk factors have also helped shape public health guidelines and direct resources. However, it is challenging to analyze and predict since they are an event that still happened. In this paper, we proposed A Study on COVID-19 Cases Analysis and Prediction with Social information and Air Quality Data Using Machine Learning. First, we will discuss the exploratory data analysis of COVID-19 cases reported. Second, we are going to compare several forecasting methods, such as statistical and neural networks. We will also figure out the uncover COVID-19 relationships, such as social media information, COVID-19 testing, several world index factors, and air pollutants, also demonstrated in this paper.

**Keywords:** COVID-19, Analysis and Prediction, Disease monitoring, Public health, Machine learning

**鼻黏液中抗微生物胜肽在免疫功能的角色：鼻黏液麴菌孢子發芽抑制的研究**

Protective effect of antimicrobial peptides in nasal secretion: impact on germination of conidia of *Aspergillus*

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鼻黏液是呼吸道的第一道防線。黏液中含有脂質、多糖體、抗微生物胜肽等物質。鼻腔的黏液纖毛功能，上皮緊密結合，及鼻黏液中抗微生物胜肽 (antimicrobial peptides) 屬於先天免疫功能，是人類鼻腔上皮屏障功能的三個主要角色。鼻黏液中抗微生物胜肽、抗體種類繁多且相關研究很少，文獻報告疾病狀況和治療會影響鼻腔抗微生物胜肽的組成或含量。本研究希望透過觀察受試者鼻黏液在體外抑制孢子發芽的能力，及鼻黏液中組成的差異，了解免疫不全患者易有呼吸道感染的可能機轉。

收案健康自願者和免疫不全者，收集患者的鼻腔灌流液。觀察麴菌孢子在兩組患者的鼻黏液中發芽動態，並分析鼻黏液中蛋白質的組成。

初步的結果觀察到不同免疫狀況者，鼻腔症狀類似，但鼻腔中收集的黏液與黴菌孢子混合後，孢子發芽狀況有顯著的不同。後續的研究，希望綜合目前的觀察結果，並透過鼻腔黏液蛋白質分析的結果共同的解讀，並設計進一步的實驗了解鼻腔黏液抑菌的機轉，瞭解鼻腔發炎性疾病的可能預防方式。

**關鍵字：**抗微生物胜肽，呼吸道，真菌、感染，鼻黏液

Nasal mucus is the first line defense barrier against a variety of inhaled pathogens. Nasal mucus consists of a variety of lipids, glycoconjugates, cells, and proteins. Mucociliary function, epithelial tight junction, and antimicrobial peptides are the three main components of mucosal innate immunity for maintaining barrier function. Various kinds of antimicrobial peptides and immunoglobulins had been identified in human nasal mucus. Studies investigating nasal mucus are few. It had been reported that host immunity status and treatment modality could alter the composition of nasal antimicrobial peptides. In the current study, we collected nasal lavage fluids from health volunteers and immunodeficient subjects. *Aspergillus* conidia were co-cultured with their nasal mucus. The percentage of germination of *Aspergillus* conidia was calculated and compared between groups. In addition, the composition of antimicrobial peptides from each group were analyzed. The purpose of this study was to investigate the mechanisms of airway fungal infection in immunocompromised hosts.

Nasal lavage was collected from immunocompromised and healthy subjects. The lavage fluid was pooled for protein analyses. In addition, fungal conidia were coculture with the nasal

lavage. The germination rates of conidia and growth pattern were analyzed as well.

We found that the protein compositions are different between healthy and immunocompromised subjects. In addition, germination rate and growth pattern were different among immunocompromised subjects with different underlying diseases.

**Keywords:** antimicrobial peptide , airway , infection , fungus, nasal secretion

## TCVGH-T1107805

### 應用臨床大數據分析建立慢性腎臟病患者腹膜運輸功能長期變化趨勢之預測模型

Construction of a model for predicting long-term trend of peritoneal membrane transport function in patients of chronic renal diseases by analyzing clinical big data

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長期腹膜透析會導致患者腹膜結構及功能性的改變，因此需要長期的研究幫助判斷什麼類型的病人較可能會發生這些變化。本研究的目的是在評估腹膜透析病人之技術存活率與其不同起始腹膜通透性之相關性、以及與各種疾病背景之關係。我們蒐集了 268 位 2014 年 1 月至 2019 年 12 月間接收腹膜透析 3 個月以上的病人的資料，他們的腹膜平衡功能數據經過電腦程式執行合併、清理、平移、以及運算之後用以觀察他們腹膜運輸功能之變化，並用以發掘他們技術存活率與起始運輸功能分組之關聯性。數據分析結果顯示腹膜透析進行兩年內，腹膜通透性高及低這兩組有向中間集中的趨勢。起始腹膜通透性不同的組別只有在腹膜透析進行的第一年有顯著的技術存活率差異( $p = 0.151$ )，但無實際生存率之差異( $p = 0.151$ )。在腹膜透析的六年中，慢性腎絲球炎患者起始腹膜通透性不同組別在技術存活率有顯著的差異( $p = 0.012$ )，而高血壓( $p = 0.067$ )及糖尿病( $p = 0.695$ )族群則無此差異性。總體而言，我們的分析顯示腹膜透析之患者在兩年之內的預後良好，但未來我們需要更多來自不同機構及疾病背景之腹膜透析研究資料來確認我們目前的結論。

**關鍵詞：**腹膜透析、腹膜平衡測試、技術存活曲線、透析清除濾

Long-term peritoneal dialysis (PD) results in structural and functional changes in the peritoneum. Longitudinal studies are thus needed to help identify which patients might develop the changes. The aim of this study was to prospectively evaluate patients' technique survival in different peritoneal transport status as well as the potential correlations with disease entities. We recruited 268 patients on PD for more than 3 months between January 2014 and December 2019, their peritoneal equilibration test (PET) data were combined, cleaned, aligned, and processed with computer programs to observe their long-term transport evolution of peritoneum and to correlate the patient and technique survival with initial peritoneal transport categories. Data analysis revealed a trend that high and low permeability groups will evolve toward the average within two years. Patients with different permeability in the first year of PD had significant difference in the technique survival ( $p = 0.006$ ), but not in patient survival ( $p = 0.151$ ). Within six years of PD, chronic glomerulonephritis (CGN) patients with different



permeability had a significant difference in the technique survival ( $p = 0.012$ ), but not in hypertension (HTN) ( $p = 0.067$ ) and diabetes (DM) ( $p = 0.695$ ) groups. In conclusion, our data indicated that patients had relatively better outcome within two years of PD, however, we need more population with different institutes and disease entities to expand PET evolution to validate these results.

**Keywords :** Peritoneal dialysis, peritoneal equilibration test, technique survival, KTV

## **以弱監督深度學習為基礎之白斑症治療評估系統建置**

A Vitiligo treatment evaluation system based on weakly supervised deep learning technique

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白顛風(白斑症)是最常見的色素沉著症。白顛風的患病率在全球人口中約有 0.5%~1%，大大影響了患者的生活品質。目前已採用各種治療方法對治這種皮膚病。由於缺乏一共同可靠之評估方法，使得無法評估不同的治療方法或相同療法對不同病患之療效。最近，許多半客觀評價系統廣泛使用手掌 1%規則來估算病灶的表面積。例如，VETF 合併分析程度，疾病階段和病變進展，其中程度之估算是最重要部分。透過使用患者的手掌單位佔病變部位的 1%身體表面積。VASI 也將此規則與色素沉著程度以提供疾病嚴重程度指數。但是，在估算面積時，這些方法依靠視覺評估，需要一定程度的主觀干預。直到最近，研究人員才試圖探索較少主觀干預的新面積測量，例如點數計算方法，和數字化方法等。然而，特殊的設備軟體需求和低效率的操作使這些方法不切實際。例如，將透明紙放在病變和邊界用鋼筆勾勒出輪廓，然後透過 CAD 軟體或透過計數點來測量格子面積轉換成患部面積。因此，如果將上述這些方法應用於大量患者的真實臨床場景將造成醫護很大之負擔。

此外，現有的技術存在以下的問題：(1) 過渡區模糊且色素沉著之間的對比度較低和色素沉著的皮膚；(2) 各種不受控制的照明成像條件；(3) 出現偽影（例如，頭髮，反射，陰影和衣服）；(4) 缺乏大型資料集有效的模型學習（例如深度學習）(5) 拍攝條件之變異，如光源、攝影角度等。本計畫提出以下研究方法，嘗試提供皮膚病醫師一個自動有效之病變區域之評估方法及系統。(1)使用伍式燈將患者之患部與正常部位一併收集拍照，建立一龐大影像庫。(2)提出了一個新穎的弱監督框架，通過三階段逐步建置一可靠自動化程度高之評估系統。第一階段從大面積影像如頭臉部等，使用 CNN 深度學習之副產品 activation map 初步分切出患部。第二階段使用少量醫師標記認證之患部圖像，將大量伍式燈拍照之患部影像進行自我學習分類，可產生精確的患部邊界，便於評估療效。第三階段使用人臉辨識技術，進行相機拍攝角度校正，解決因不同拍攝角度造成之影像扭曲，影響患部面積計算。

**關鍵字：**白斑症、邊緣萃取、激活圖、顯著圖、弱監督學習、超像素。

Vitiligo is the most common pigmentation disorder. The prevalence of vitiligo in the global population is about 0.5% to 1%, which greatly affects the quality of life of patients. Various treatments have been used to treat this skin condition. The lack of a common and reliable assessment method makes it impossible to assess the efficacy of different treatments or the same therapy in different patients. Recently, the palmar 1% rule has been widely used by many semi-objective evaluation systems to estimate the surface area of lesions. For example, the VETF pooled analysis of extent, disease stage, and lesion progression, with the estimation of extent being the most important part. By using the patient's palmar unit occupies 1% of the body surface area of the lesion. VASI also associates this rule with the degree of pigmentation to provide a disease severity index. However, when estimating area, these methods rely on visual assessment and require some degree of subjective intervention. Only recently have researchers attempted to explore new area measurements with less subjective intervention, such as point counting methods, and digital methods. However, special equipment software requirements and inefficient operation make these methods impractical. For example, place a transparent paper on the lesion and the boundary and outline the outline with a pen, and then measure the grid area through CAD software or by counting points and convert it into the area of the affected area. Therefore, if these methods are applied to real clinical scenarios with a large number of patients, it will cause a great burden on medical care.

In addition, the existing techniques suffer from the following problems: (1) blurred transition zones and low contrast between pigmentation and hyperpigmented skin; (2) various uncontrolled lighting imaging conditions; (3) appearance of artifacts ( For example, hair, reflections, shadows, and clothes); (4) Lack of effective model learning (e.g. deep learning) for large datasets; (5) Variation in shooting conditions, such as light source, camera angle, etc. This project proposes the following research methods in an attempt to provide dermatologists with an automatic and effective assessment method and system for lesion areas. (1) Use the Wu-style lamp to collect and take pictures of the affected part and the normal part of the patient to build a huge image library. (2) A novel weakly supervised framework is proposed to gradually build a reliable and highly automated evaluation system through three stages. The first stage uses the activation map, a by-product of CNN deep learning, to preliminarily cut out the affected part from large-area images such as the head and face. In the second stage, a small number of doctor-marked and certified images of the affected area are used, and a large number of images of the affected area photographed by the Wu-style lamp are used for self-learning and classification, which can generate accurate boundaries of the affected area and facilitate the evaluation of the curative effect. The third stage uses face recognition technology to correct the shooting angle of the camera to solve the image distortion caused by different shooting angles, which affects the calculation of the affected area.

**Keywords:** vitiligo, edge extraction, activation map, saliency map, weakly supervised learning, super-pixel

## TCVGH-T1107807

### 合成並評估苯並雜卓類化合物作為胱氨酸-麩氨酸反向轉運蛋白調節劑

Synthesis and evaluate benzazepine compounds as system xc- modulators

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胱氨酸-麩氨酸反向轉運蛋白在維持細胞內麩胱甘肽的濃度扮演了重要的角色。然而在氧化壓力的刺激下，此反向轉運體的功能會上調，導致麩氨酸外排也相對增加。麩氨酸外排的增加通常會造成神經興奮性毒性，有研究證實如此會導致神經細胞的死亡。胱氨酸-麩氨酸反向轉運蛋白也會影響腫瘤的微環境，大腦中癌細胞藉由釋放麩氨酸毒殺周遭神經細胞，並增加細胞內麩胱甘肽的濃度，修復任何化療或是放射線治療帶來的傷害。Fazzari 等作者曾對於分子庫進行胱氨酸-麩氨酸反向轉運蛋白調節劑篩選，發現其中有數個藥物具有抑制活性。我們進一步發現其中幾個藥物皆具有苯並雜卓結構骨架，因此於此計畫希望藉由合成此類型衍生物，找到具有良好調節效果的化合物。

**關鍵詞：**胱氨酸-麩氨酸反向轉運蛋白、苯並雜卓、抑制劑

System xc- plays an important role in maintaining elevated intracellular levels of glutathione. However, under oxidative stress, it is upregulated resulting in enhanced efflux of glutamate and subsequent excitotoxicity. The excitotoxicity has been shown to cause neuronal death. System xc- also affects the tumor microenvironment, giving cancer cells in brain tumors a survival advantage over neurons. Fazzari et al. screened the molecular library for cystine-glutamate antiporter modulators and several drugs showed inhibitory activity. We have further discovered that a few of these drugs possess benzazepine core structure. In this project, we wish to find more effective cystine-glutamate antiporter modulators through synthesizing some benzazepine derivatives.

**Keywords:** system xc-, cysteine-glutamate antiporter, inhibitor, benzazepine

## **COVID-19與社群網媒對健康照護體系之衝擊分析**

Impact of COVID-19 and Social Media on Health Care System

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面對新型冠狀病毒(COVID-19)疫情肆虐並經由社群網媒(Social Media)對重大疫情的報導，導致全球經貿環境與健康照護體系遭受嚴峻挑戰。政府對醫院之疫情控管措施及就醫者對網媒訊息所產生之恐懼效應，勢必衝擊民眾就醫意願。本計畫以台中榮民總醫院之就醫需求資料庫(門診、住院、健檢、四癌篩選、遠距問診)，首先利用 2019 及 2020 年 1 月~9 月之日資料，利用兩母體平均數差異性 t 檢定及多母體 F 檢定，發現 2020 年疫情會顯著降低民眾就醫需求，且會因科別而存在不同程度之差異性；其次，利用 Poisson 整數計次資料迴歸模型，發現 COVID-19 負面重大訊息、台灣每日新增確診數、第 1 及 2 季(相對於第 3 季)，會顯著降低健康照護利用率；最後，在遠距醫療方面，問診人次由 2019 年之 6 人增至 2020 年之 68 人，顯示重大疫情會擴大智慧醫療需求但績效仍待提昇。

**關鍵詞：**COVID-19、社群網媒、健康照護體系、Poisson 整數計次資料迴歸模型

Global health and economic systems encounter a destruction on an unprecedented scale in the fight against Covid-19. Measures taken by governments and misinformation spread across social media have prevented citizens to seek medical treatment in the health systems to some degree. The research project utilized Taichung Veterans General Hospital database to study the medical demand of outpatient, inpatient, health checkup, cancer screening, and long-distance medical care during 2019-2020. We found that the situation of outbreak has a significant impact on citizen's willingness to visit hospitals, but there exist different degrees of influences among divisions. In a Poisson integer-count-data regression model, we also found that major negative news on Covid-19, the number of Taiwan's daily confirmed cases, the first and second quarter of 2020 compared to the third quarter have shown a negative effect on the hospital's utilization. Finally, the number of people utilizing long distance medical care increased from 6 people in 2019 to 68 people in 2020. This suggests that the pandemic increases the demand of smart healthcare; however, the efficiency of such medical care requires further investigation.

**Keywords:** COVID-19, Social Media, Health Care System, Poisson Integer-Count-Data Regression Model

**透過服務設計改善住院兒童復原力、希望與期望之研究—以VR體驗為例**

Research on Improving Hospitalized Children's Resilience, Hope and Expectation Through VR Experience

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隨著虛擬實境 (VR : Virtual Reality) 技術逐漸趨於成熟，VR 已漸漸成為提升兒童住院體驗的有力工具。住院，會為兒童帶來各種在醫療、心理和情感方面的挑戰。而恢復力則是一種能讓個人能夠成功應對生活中困難的能力。擁有高希望感的人通常也會有較高的恢復力。過去的研究也指出病人的希望與較好的醫療結果具有相關性。然而，目前尚缺乏關於兒童對 VR 應用的心理認知與理解，以及對住院兒童的希望狀態探討之研究。因此，本研究提出兩項研究問題:(一)VR 應用於觀光景點是否可以為住院兒童帶來愉悅性的感受?(二)VR 應用於觀光景點是否可以提升住院兒童的恢復力、希望與期望?

本研究使用實驗法，透過問卷設計了解兒童於 VR 體驗後希望感之差異，並以生理數據收集測量兒童於 VR 體驗時實際的興奮程度與效果。研究結果表示，VR 應用於觀光景點可以為兒童帶來愉悅性體驗，同時，也可提升兒童的希望與期望。於是本研究提出兩個研究結論:(一)VR 應用於觀光景點可做作為提供住院兒童正向愉悅情緒的來源之一。(二)住院兒童希望較健康兒童更難被激發。

在實務上，本研究提供利用 VR 進行心理輔助的方法，讓醫護人員和家長進行彈性運用。在學術上除了提出 VR 應用在兒童心理照護的有效性外，也進一步運用希望感理論衡量 VR 應用之效果，並提出健康兒童與住院兒童在愉悅與希望感認知上的差異，以供未來學者進行住院兒童心理認知相關研究時之參考。

**關鍵詞：**愉悅感、希望感、復原力、VR 應用、ECG

Nowadays, VR (Virtual Reality) has gradually become a powerful tool for enhancing patient experience in the children's wards. Hospitalization will bring various medical, psychological, and emotional challenges for children. Resilience enables individuals to take on life's challenges successfully. People with high hopes usually have higher resilience. Past studies have also pointed out a positive relationship between hope and treatment. However, there is a lack of research on hospitalized children's psychological cognition of VR applications and the inquiry about the hope state of hospitalized children. Therefore, the following questions are proposed: (1) Can VR application in tourist destinations bring a pleasurable experience for hospitalized children? (2) Can VR application in tourist destinations enhance hospitalized children's resilience, hope, and expectations?

The experimental method is used in this research. The questionnaire is designed to understand the difference in children's hope, then collecting the physiological data through ECG to understand children's excitement. The results indicate that VR can bring the pleasurable experience and enhance children's hope and expectations. Therefore, two conclusions are proposed: (1) VR can be used as one of the sources of positive emotions for hospitalized children. (2) The sense of hope is more difficult to be stimulated for hospitalized children than healthy children.

This research provides a method of using VR for psychological assistance and allowing medical staff and parents to use it flexibly. Academically, this research determines the feasibility of VR in children's psychological care, uses the sense of hope to measure the effect, and then proposes the difference between healthy and hospitalized children in pleasure and hope.

**Keywords:** Pleasure, Hope, Resilience, Virtual reality, ECG

## TCVGH-T1107810

### 通過機器學習，從心臟超音波大數據資料庫預測心臟衰竭患者接受節率器治療的預後

Echocardiography big data predict prognosis of heart failure patient received CRT treatment, by machine learning

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本研究追蹤心臟病患看診後三年的診療情況，治療方式分為心導管電燒術、心室去顫器、藥物控制，將資料分為 9 類後，使用非監督式學習與監督式學習訓練資料，非監督式使用 7 種演算法及監督式學習 2 種演算法，最後透過遞迴特徵消除篩選重要特徵，比較四種不同特徵數量對準確度的影響，在準確度方面監督式學習的準確度最高為 1，而非監督式最高準確度約為 0.44，特徵選取後的準確度相比較原始資料的變化差異不大，演算法中 XGBoost 的準確度為最高。

**關鍵詞：**心電圖,非監督式學習,監督式學習,分類,心率不整

This study tracks the diagnosis and treatment of heart disease patients with three years historical data after seeing the doctor. The treatment methods are divided into cardiac catheterization, ventricular defibrillator, and drug control. After the clinical data is divided into 9 categories, both unsupervised and supervised learnings are uses to train the best feasible model based on training data. Unsupervised and supervised learnings use 7 and 2 algorithms, respectively, through recursive features to eliminate and filter important features out. The judgement based on the model accuracy for supervised learning and the comparison of four different features' impact on accuracy for unsupervised learning. The highest accuracy for supervised learning is 1, while the highest accuracy of the unsupervised model is about 0.44. The accuracy of feature selection is not much different from the original data. This study shows the XGBoost algorithm possess the highest accuracy.

**Keywords :** echocardiograms, unsupervised learning, supervised learning, classification, catheter ablation.



## TCVGH-T1107811

### 探討合成胜肽之抗異位性皮膚炎功效 (II)

Investigation of Anti-atopic Dermatitis Effects of Synthetic Peptides by in vitro Cell Culture Models (II)

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異位性皮膚炎 (AD) 是最常見的慢性過敏性皮膚病之一，其致病原因受到多種遺傳和環境等因素交互作用而十分複雜。最近的臨床研究發現在許多 AD 患者中，呼吸道過敏原對於誘發濕疹樣病變扮演關鍵的角色。已知皮膚角質細胞會受到各種環境因子的刺激而被激活並釋放出多種 AD 相關的細胞發炎因子。先前，我們建立了蟑螂過敏原誘導的 HaCaT 角質細胞平台來模擬與 AD 相關的炎症。LT 系列胜肽是實驗室中具有潛力的抗菌胜肽 HDM-2 之衍生物。本研究目的是應用 rPer 10 刺激的角質細胞平台評估 LT 系列胜肽的抗發炎作用並探討其分子機制。我們已進行 6 條 LT 系列胜肽的細胞毒性測定，並應用 rPer 10 刺激的 HaCaT 細胞平台評估其抗發炎效果。其中，LT-1 不僅顯著地抑制蟑螂過敏原 rPer 10 刺激角質細胞後的發炎指標 IL-8、CCL-20 和 GM-CSF 等基因的表現，且具有較高的生物安全性。因此，LT-1 被認為是治療皮膚發炎疾病具有潛力的候選藥物。在這次報告中，為了提高 LT-1 胜肽的產率，我們使用了 2 種胜肽裂解試劑 (reagent K 與 reagent R)，並調整其試劑組成與反應時間 (2 小時與 4 小時)。結果顯示，使用含有 90% TFA 的 reagent K 並裂解胜肽 4 小時，有效的切除胜肽側鏈保護基團，提高 LT-1 的產率 (產率約達 60.9%)。此結果為隨後的抗發炎機制實驗建立了胜肽量產的最佳化條件。IL-8 是 AD 局部皮膚損傷嚴重程度的代表性指標。LT-1 顯著抑制 Per a 10 誘導的 HaCaT 細胞中 IL-8 的表達，甚至優於治療炎症性皮膚病的皮質類固醇 dexamethasone。MAPK 是發炎反應最主要的細胞訊息傳遞途徑，透過 ERK1/2、JNK 和 p38 MAPK 的磷酸化進而調節 MAPK cascades。我們進一步研究了 LT-1 對 MAPK 途徑的影響。初步結果發現，LT-1 顯著抑制 Per a 10 誘導的 HaCaT 細胞中 ERK、JNK 和 p38 的磷酸化。許多研究表明，在 AD 皮膚病變中發現抗菌胜肽 (AMP) 的水平降低，解釋了 AD 相關感染的高發生率。有趣的是，LT-1 治療可以增加角質形成細胞中人類  $\beta$ -防禦素 3 (HBD3) 的表達。最後，這些數據證實了 LT-1 在皮膚治療中具有有益的作用，而詳細分子機制正在研究中。

**關鍵詞：**異位性皮膚炎、慢性過敏性皮膚病、呼吸道過敏原、皮膚角質細胞、蟑螂過敏原、慢性炎症、抗微生物胜肽、抗菌胜肽

Atopic dermatitis (AD) is one of the most common chronic allergic skin diseases, and its pathogenesis is very complicated due to several genetic and environmental factors. Recent evidence demonstrates that aeroallergens play an essential role in the elicitation of eczematous lesions in many AD patients. Keratinocytes are known to be activated by a variety of environmental stimuli and to release several cytokines contributing to the development of AD. Previously, we have developed a cockroach allergen-induced HaCaT cell platform to mimic the AD-related inflammation. LT series peptides are HDM-2 peptide analogues with potential antibacterial activity. In this study, we aimed to evaluate the anti-inflammatory effects and molecular mechanisms of LT series peptides in rPer a 10-stimulated keratinocytes. First, we performed a cytotoxicity assay and evaluated the anti-inflammatory activities of the six LT series peptides in rPer a 10-stimulated HaCaT cells. Among them, we found that LT-1 was not only significantly inhibited rPer 10-activated gene expression of IL-8, CCL-20, and GM-CSF in the HaCaT cells but also possessed less toxicity to cells. Therefore, LT-1 is considered to be a potential medicine candidate for the treatment of inflammatory skin diseases. In this year's report, in order to improve the yield of LT-1 peptides, we used two Fmoc cleavage cocktails (reagent K and reagent R) for cleavage and adjusted their reagent composition and reaction time (2 hours and 4 hours). The results showed that using reagent K containing 90% TFA and cleaving the peptide for 4 hours effectively cleaved the side chain protecting group of the peptide and improved the yield of LT-1 (about 60.9%). This result established the optimal conditions for the large-scale production of peptides for the subsequent anti-inflammatory mechanism experiments. IL-8 is a representative indicator of local severity in skin lesions of atopic dermatitis (AD). LT-1 was found to significantly inhibit the expression of IL-8 in Per a 10-induced HaCaT cells, even better than dexamethasone which is a corticosteroid used in treating many inflammatory skin conditions. The MAPK pathways represent the major intracellular signaling of the degree in inflammation. ERK1/2, JNK, and p38 MAPK regulate MAPK cascades through phosphorylation. Many studies have shown a reduced level of antimicrobial peptides (AMPs) in AD skin lesions, explaining the high frequency of AD-related infections. Interestingly, peptide LT1 treatments could increase the expression of human beta-defensin-3 (HBD3) in keratinocytes. Taken together, these data provide evidence for a beneficial role of peptide LT-1 in skin therapy. Further studies for detailed molecular mechanisms are in progress.

**Keywords** : Atopic dermatitis, aeroallergens, keratinocyte, cockroach allergen, chronic inflammation, antimicrobial peptides (AMPs), antibacterial peptides (ABPs)

#### 人工智慧應用於護理人員於執業環境之壓力分析:以台中榮民總醫院外科病房為例

Pressure Analysis of Nurses on Practice Environment Using AI: Taking Taichung Veterans General Hospital for Example

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職業壓力和工作過勞一直是護理人員會普遍遇到的問題，隨著疫情發展，許多醫護人員選擇留在前線，承受自己可能被傳染的高風險，一方面要安撫恐慌患者，另一方面還要承受家屬的求、責難以及外界社會所給輿論壓力。長期在高壓緊張的環境下工作，在照看病人同時卻常忽略了自己身體出現警訊。

目前市面上穿戴式健康智慧監測工具已發展成熟，本研究以無線個人區域網路 (Wireless Personal Area Network, WPAN) 為基礎，建構護理人員生理資訊蒐集與分析系統。護理人員配戴智慧型手環，透過自主性及長期的健康監測，將護理人員的生理資訊及職場環境狀態等相關料，運用物聯網 (Internet of Things, IoT) 技術匯入雲端資料庫中，透過視覺化 (Data visualization) 及機器學習 (Machine Learning) 的監督式學習演算法，進行數據的整理與分析，讓護理站能隨時了解人員狀況，作為即時調動人力的參考。

**關鍵詞：**護理師、健康管理、智慧型穿戴裝置、物聯網、人工智慧、機器學習、壓力來源分析

Occupational stress and overwork have long been common problems for caregivers. As the outbreak develops, many healthcare workers choose to stay on the front lines, carrying the risk of being exposed to the high risk of being infected. Their work involves the need to not only appease the panicked patients, bear the demands and censures of patients' family members, but face the pressure of public criticism from society. Working in a high-pressure environment for a long time while taking care of patients, the healthcare workers often miss the warning signs of their health status.

At present, smart wearable devices on the market have developed rapidly. In this study, we first construct a data acquisition and analysis system for nurses' psychosocial and physical signal based on Wireless Personal Area Network (WPAN) system. Healthcare workers were asked to wear smart bracelets. Through autonomous and long-term health monitoring, data such as nurses' physiological information and workplace environment status were applied to

the Internet of Things (IoT) technology, which was later imported into the cloud database. The data is then organized and analyzed through the supervised learning algorithm of data visualization and machine learning so that the nursing station can follow the health status of each healthcare worker at any time, making it a reference for an immediate personnel change.

**Keywords :** Nursing, health management, smart wearable devices, IoT, artificial intelligence

## 人工智慧協助子宮內膜切片診斷

Artificial intelligence-assisted diagnosis in endometrial biopsies

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### 背景:

子宮內膜檢體在病理診斷上為常見且重要的檢體，可以提供子宮內膜情形與診斷給臨床醫師，並幫助臨床醫師做出正確的處理及治療。子宮內膜在低倍顯微鏡下以格局型態做診斷依據，並在高倍鏡檢下觀察細胞的型態與變化，以此做出正確診斷。目前數位病理及人工智慧的進步可加速且更有效率幫助正確診斷。此研究計畫用深度學習工具，幫忙子宮內膜型態辨識，把診斷粗略分為正常、增生及癌性變化。

### 方法:

子宮內膜檢體玻片去辨識並數位掃描後，圈出具有診斷性的位置。接著把具診斷性的影像作深度學習，訓練電腦判讀型態。經過反覆的影像訓練，再測試是否電腦可以正確把新的個案檢體分至正確的組別。

### 結果:

電腦深度學習後的分類與病理醫師的診斷比較，可以得知診斷的正確性。此深度學習工具可作為子宮內膜切片病理診斷的輔助工具。

**關鍵詞：**子宮內膜切片、人工智慧、深度學習、子宮內膜增生、子宮內膜癌

### Background:

Endometrial tissue specimens are commonly encountered in daily practice of pathology. The pathologic diagnosis is pivotal to inform clinical physicians about medical conditions, such as normal, infection, hyperplasia, and neoplasia and prompt optimal managements. Accurate pathologic diagnosis relies on pattern recognition at low magnifications and cytomorphic evaluation at high magnifications. Recent advances in the techniques of whole slide imaging and artificial intelligence have proved to facilitate pattern recognition and image interpretation. The study aims to utilize deep learning model to aid pattern recognition in endometrial samples, classifying the diagnosis into normal, hyperplastic and neoplastic categories.

### Method:

Endometrial samples are scanned and the targeted areas are gated on the whole slide images. The images are then uploaded to a training algorithm that makes creating a machine learning model. Repeat training and testing out the model to ensure the computer can correctly classify new examples.

**Result:**

The accuracy of classification will be evaluated by comparing the results by computer-based tool with the diagnosis made by pathologists. Larger scale of study will be planned if the preliminary results are convincing. The model can further be used in aiding the pathological diagnoses of endometrial specimens.

**Keywords :** endometrial biopsy, artificial intelligence, deep learning, endometrial hyperplasia, endometrial carcinoma.

### 利用小波包轉換與自適應共振理論於動靜脈瘻管狹窄程度分類之研究

Classification of Arteriovenous Fistula Stenosis States Using Wavelet Packet Transform and Adaptive Resonance Theory

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本研究期望透過簡易、方便、準確且非侵入式的監測方式，嘗試找到動靜脈瘻管訊號與瘻管狹窄位置之關聯性，並對於瘻管狹窄程度分析與預測。在研究方法上，硬體部分我們採用音頻感測器擷取受試者瘻管上方的訊號至筆記型電腦，而軟體部分則以自行開發之 LabVIEW 程式連接感測器，並進行訊號的擷取與儲存，後續之訊號分析與分類則採用自適應共振理論網路以自動分類狹窄或阻塞的音頻訊號。經過本次研究發現，若採用自適應共振理論網路予以自動分類，其判斷狹窄或阻塞的準確率不高，因此我們改為使用瘻管上方的音頻訊號作為判斷的依據，採用連續小波分析後的圖形送入卷積神經網路(CNN)進行訓練與測試得到較好的結果。本研究計畫之取樣及資料收集皆在台中榮民總醫院之血液透析室進行，實際用於結果測試之資料筆數為正常 14 例、狹窄 20 例、阻塞 10 例共計 44 例，採用其音頻訊號並做連續小波分析後的圖形送入卷積神經網路，將正常、阻塞及狹窄分為三類，最後實驗結果之準確率 77.3%。

**關鍵詞：**小波包轉換、自適應共振理論、血液透析、自體動靜脈瘻管、卷積神經網路、音頻感測器

This study aims to find the correlation between the arteriovenous tract signal and the fistula stenosis position through a simple, convenient, accurate and non-invasive monitoring method, and to analyze and predict the fistula stenosis degree. In the hardware part, an audio sensor was used to capture the signal above the subject's fistula and send to the notebook computer. A self-developed LabVIEW program was used in the software part to connect the sensor and perform signal acquisition and analysis. For subsequent signal analysis and classification, the adaptive resonance theory network was used to automatically classify narrow or blocked audio signals. The results revealed that if the adaptive resonance theory network was used for automatic classification, the accuracy of judging stenosis or obstruction was not high. Therefore, we changed to use the audio signal above the fistula as the basis for judgment. The wavelet transform of the audio signal was sent to the convolutional neural

network (CNN) for training and testing to obtain better results. The sampling and data collection of this research project were all carried out in the hemodialysis room of Taichung Veterans General Hospital. Totally forty-four cases were recruited for this study with 14 normal cases, 20 stenosis cases, and 10 obstruction cases. The audio signal was used and the graph after continuous wavelet analysis was sent to the CNN. The convolutional neural network divides normal, obstructed and stenotic into three categories. The final result is that the accuracy reaches 77.3%.

**Keywords** : Wavelet packet transform, adaptive resonance theory, hemodialysis, arteriovenous-fistula, convolutional neural network, audio sensor.



**應用深度學習於新生兒膽道閉鎖之超音波影像辨識**

Ultrasonic image recognition of neonatal biliary atresia using deep learning

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新生兒及嬰兒延遲性黃疸(Prolonged Jaundice)是兒科及兒童外科醫師常常遇到的狀況，臨床上常用嬰兒大便篩檢卡、抽血檢查、扎足跟血檢查或利用經皮膽紅素計(Transcutaneous Bilirubinometer) 診斷或追蹤，但由於大便卡為簡易篩檢，而新生兒或嬰兒抽血不易，足跟血檢驗可信度較低並且仍具侵入性，而經皮膽紅素計乃利用光學反射原理，其數值與膚色及血紅蛋白含量有關，臨床上無法用來確診延遲性黃疸。腹部肝膽系統超音波檢查(Hepatobiliary Ultrasound)是懷疑如膽道閉鎖(Biliary Atresia)等病理性黃疸之病人必做的檢查，其優點為簡單可得且不具侵入性。但超音波檢查因執行者與判讀者之不同，所得到的影像差異性極大。且超音波用以診斷膽道閉鎖之敏感度與特异性不足以取代較具侵入性之檢查，如肝切片(Liver Biopsy)或手術中之膽道攝影(Intraoperative Cholangiography)，是以目前膽道閉鎖之診斷仍無法完全以非侵入性檢查完成，增加病人可能的風險。由膽道閉鎖而引起的黃疸及肝硬化可能致命，需要及時手術，本研究可以輔助與提醒醫生，提升非侵入式診斷的準確度，避免漏診潛在病患。

**關鍵詞：**圖像分類、膽道閉鎖、深度卷積網絡、機器學習、病理性黃疸、超音波圖像

Neonatal prolonged jaundice is a condition often encountered by pediatric surgeons. In clinical practice, infant stool card screening cards, blood tests, heel blood tests, or transcutaneous bilirubinometer are commonly used for diagnosis or tracking. However, because the stool card is a simple screening test, and it is not easy to draw blood from newborns or infants, the heel blood test is less reliable and still invasive. The transcutaneous bilirubin meter uses the principle of optical reflection, and its value is consistent with skin color. It is related to hemoglobin content and cannot be used to diagnose delayed jaundice clinically. Hepatobiliary ultrasound is a necessary diagnosis for patients suspected of pathological jaundice such as biliary atresia. It has the advantages of being easy to obtain and not invasive. However, due to the difference between the performer and the reader, the images obtained in the ultrasonic examination are very different. In addition, the sensitivity and specificity of ultrasound for diagnosing biliary atresia are not enough to replace more invasive tests, such as liver biopsy or intraoperative cholangiography, so the current biliary atresia. The

diagnosis still cannot be completely completed by non-invasive examination, which increases the possible risk of the patient. Jaundice caused by biliary atresia is fatal and requires immediate surgery. This study can assist and remind doctors to not miss potential patient.

**Keywords :** Image Classification, Biliary Atresia, Deep Convolutional Network Machine Learning, Prolonged Jaundice, Ultrasound Image

## 人工智慧技術用於麻醉前辨別異常呼吸音監測系統

Application of Artificial intelligence technology to identify abnormal breath sounds monitoring system before anesthesia

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手術前常常會安排胸部 X 光來分析病人肺部病灶，確認接收手術麻醉的病人肺部的情況。肺部病灶例如氣喘、肺炎、肺積水、肋膜積水等情況可能導致麻醉中的風險。這些疾病預先辨識出來，能夠先進行治療或準備，以減少手術後肺部併發症。聽診能夠診斷肺部病灶，並且具有非侵入性、便利性、和無放射性的優點。若能夠使用電子聽診器+人工智慧技術來分析呼吸音，預測肺部各種病灶，可以增加病人麻醉安全性，減少醫護人員近距離接觸病患，加速術前訪視中心效率。

已經有相關研究指出，聽診能夠有效辨識各種不同肺部病灶。根據前期研究已經能使用電子聽診器合併 CNN+LSTM 人工智慧網路演算法，預測使用電腦斷層標註的肺部病灶，準確性已達到 70%-85%。今年所提之計畫以最新的時序列膠囊網路理論來實踐深度類神經網路的自注意力機制膠囊網路(CapsNet)對肺部異常進行時序列監控，強化特徵的辨識訓練，以少量樣本學習並提升辨識準確度。這將為本持續研究計畫所收集的有限資料帶來更高的預期效益。

**關鍵詞：**心音診斷、肺音診斷、心雜音分析、膠囊神經網路、智慧醫療、人工智慧

Before surgery, chest X-rays are often arranged to analyze the patient's lung lesions and confirm the condition of the patient's lungs under anesthesia. Lung lesions such as asthma, pneumonia, pulmonary effusion, pleural effusion, etc. may lead to risks during anesthesia. These diseases are identified in advance and can be treated or prepared first to reduce lung complications after surgery. Auscultation can diagnose lung lesions and has the advantages of non-invasiveness, convenience, and non-radioactivity. If the electronic stethoscope and artificial intelligence technology can be used to analyze breath sounds and predict various lung lesions, it can increase the safety of patient anesthesia, reduce medical staff's close contact with patients, and accelerate the efficiency of preoperative visits to the center.

Related studies have pointed out that auscultation can identify various lung lesions effectively. According to previous studies, it has been possible to use the electronic stethoscope combined with the convolutional & long short-term memory neural networks (CNN+LSTM) algorithm to predict the lung lesions marked by computer tomography, and the

predicted accuracy has reached 70%-85%. This year, the proposed project use the novel time series capsule neural networks theory to implement the attention mechanism to monitor lung abnormalities in time series and strengthen feature recognition while training. The proposed method can improve the recognition accuracy with a small number of samples, which would make a strong benefit to this continue research project.

**Keywords :** Pediatric heart and breathing sounds, smart medical device, deep learning network, artificial intelligent.

**以機器學習實現糖尿病住院患者的精準血糖值與再住院預測**

Predicting Blood Glucose and Hospital Readmission for Diabetic Inpatient by Machine Learning

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糖尿病在台灣位居十大死因之一，每年奪走近萬條寶貴性命，即平均每小時就有一人因此死亡。過去糖尿病的發生率一直在 9~10% 左右，但國衛院統計 2019 年的盛行率已經超過 11%，患者已經超過 230 萬人，顯示臺灣與全世界一樣，糖尿病盛行率正以驚人的速度攀升。文獻指出相對於一般患者，糖尿病患者有 3 倍的住院機會，其中更有 30 % 患者需要 2 次或更多次住院。然而，血糖管理團隊需要由數名專業的內分泌或新陳代謝醫師，每天在一大早視患者生理狀況及過往數據給出治療建議，背後更需要醫療、臨床醫護及資訊領域的專家人力，團隊形成不易。本研究計畫以台中榮總在電子病歷的多年耕耘為基礎，針對以胰島素注射為主的糖尿病住院患者，透過機器學習方法進行建模與分析，目標在於糖尿病住院患者精準的個人化血糖值預測與調控，降低血糖管理團隊的負擔。

**關鍵詞：**糖尿病、血糖值、機器學習、OHDSI

According to statistics, in 2017, the diabetes is the fifth among the ten leading causes of death at Taiwan. There were 9,845 lives taken away due to the diabetes, i.e., one people died every hour in average. The incidence rate of diabetes was about 9~10% in the past; however, National Health Research Institute statistics showed that the prevalence rate has been exceeded 11%, and the number of patients has been more than 2.3 million, indicating that Taiwan is the same with the world with an amazing prevalence rate of diabetes. Previous works presented that the hospital readmission of diabetics is three times larger than general patients, and around 30% diabetics has two or more readmissions. However, the management term comprises several endocrinologists, clinical health care worker, and computer engineers to support the decision marking of therapy for diabetics in the morning, where it's hard to form such a professional team. In addition, the hospital readmission is usually related to the increase in mortality rate as well as the excessively medical loads, and the unplanned readmission is becoming an indicator for healthy measurement. Taichung Veterans General Hospital performs great work to collect and store diabetic data with standard OHDSI/OMOP CDM. Based on these medical data of high quality, the project goal is to predict blood glucose for diabetic inpatient by machine learning methods.

**Keywords :** diabetes, blood glucose, machine learning, OHDSI

**以深度學習實現以最少生理訊號識別睡眠呼吸中止症類型之研究**

A study for recognition the type of sleep apnea with the least physiological signals by deep learning

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睡眠呼吸中止症候群 (Sleep apnea-hypopnea syndrome, SAHS) 是一群在睡眠時呼吸道狹窄或者呼吸驅動力降低而造成氣流無法進出呼吸道的症候群。由於睡眠時因為反反覆覆的缺氧以及睡眠的片段，造成了白天的嗜睡、心律不整以及循環系統的發炎跟免疫力的改變，長時間下來則與高血壓、糖尿病跟憂鬱等產生了共病症。因此，盡早診斷並給予正確的治療，是打破此循環鏈最好的方法。

不同類型的呼吸中止，採取的治療策略有所不同，而整夜睡眠多項生理檢查 (Polysomnography, PSG) 是最標準的分類方法。然而，這樣的檢查除了昂貴外，排程也相當冗長。我們先前發表了以嗜睡問卷、身體質量指數跟睡眠前後血壓差，以類模糊神經系統來作為中重度睡眠吸中止之快速預測，雖然有約 83.3% 的準確度，但並無法作分類；另外，我們先前也利用單一溫度感測器來作為阻塞 (apnea) 與淺呼吸 (hypopnea) 的偵測，但對於中樞型睡眠呼吸中止則未進行探究。因此，本計劃在此基礎之上，融合肺音與呼吸運動訊號，透過時域頻率分析 (Short-term Fourier Analysis) 與時頻生物融合技術來進行分類，以提供簡易篩檢工具。

研究結果顯示，在總次數 4663 次的不同類型呼吸障礙事件中，可以預測到 3756 次，對於中重度睡眠吸中止之準確度可以達 83% 之準確度，然類型的分析，仍在分析中。預期以偵測呼吸音之麥克風訊號與呼吸運動訊號，將可以做為中重度睡眠呼吸中止之篩檢以及配戴睡眠陽壓呼吸器之效果的監控工具。

**關鍵字：**睡眠呼吸中止症候群；整夜睡眠項生理檢查；時域頻率分析；生物融合

Sleep apnea-hypopnea syndrome (SAHS) is a group of syndromes with the airways are narrow or the driving force of breathing is reduced during sleep. Due to repeated hypoxia and sleep fragments in sleep, daytime excessive sleepiness, arrhythmia, inflammation of the circulatory system, and changes in immunity are caused. After a period of time, it will cause comorbidities such as high blood pressure, diabetes, and depression. Therefore, early diagnosis and correct treatment is the best way to break the effect chain.

Different types of SAHS have different treatment strategies, and the overnight Polysomnography (PSG) is the gold standard classification method. However, such diagnosis is not only with high cost but also with long time waiting list. We previously published a neural fuzzy system as a rapid prediction of moderate to severe SAHS with sleepiness

questionnaire, body mass index and blood pressure difference before and after sleep. Although it presented an accuracy of about 83.3%, it cannot classify types. In addition, we proposed a single thermocouple sensor to detect apnea and hypopnea, but we did not explore the central type of sleep apnea. On this basis, this aim of the project will integrate lung sounds and respiratory motion signals with Short-term Fourier Analysis and biological fusion to classify SAHS as to provide a simple screening tool.

The results of the study showed that the total number of 4663 different types of breathing disorder events, 3756 events can be predicted based on our algorithm and there was of the accuracy of 83% for classify moderate to severe SAHS. However, the type of analysis is still under analysis. It is expected that the microphone signal and breathing motion signal of breathing sound can be used as a screening tool for moderate and severe SAHS and the monitoring the effect of treatment of positive airway pressure (CPAP).

**Keywords:** Sleep apnea-hypopnea syndrome; Polysomnography; Short-term Fourier Analysis; Biological fusion

## 榮開計畫

### TCVGH-NK1109001

#### 開刀房護理人員排班系統(IV)

Working room nursing staff scheduling system (IV)

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護理人員排班是每位護理長每月需面臨的問題，而輪值班表的好壞，攸關護理服務的品質與人員工作的士氣。因此，設計護理人員排班系統是相當實用與重要的課題。以往班表的管理都是護理長以人工的方式進行調度，即是由護理人員自行排定上班時段及休假期，再由管理者做最後的統整，雖然人員的自主性提高，但是由於班表的數據資料龐大，考慮的因素又多，因此非常的費時費力，沒有效率，再加上用人工的方式，很難做到公平公正，影響人員的工作效率。

在本計劃中，我們開發設計排班系統，提供人員資料管理、國定假日管理、公休換班管理、自動排班、排班需求管理、排班統計、班表輸出等功能。在系統介面方面，我們做到人員在處理排班問題時就像上網一樣簡單，降低人員操作的困難度。在使用者端系統，我們設計開發 App 供護理人員使用。護理長或相關的排班人員可以直接將班表透過智慧型手機發佈給護理人員，利用 App 取得班表資訊並提供相關的功能。在演算法核心方面，我們配合個案的特性，在符合醫院政策、人員偏好、政府法規等等限制的前提下，達公平與自主的目標。

**關鍵字：**排班、App

Nursing staff scheduling is an issue of each caregiver every month. The duty schedule is good or bad that reflects the quality of care services and staff morale. Therefore, the design of nursing staff scheduling system is quite practical and important subject. In the past, the duty schedule was down by the chief care office. The data of duty schedule is huge and the factors considered are so much that it takes time and laborious.

In this program, we have developed a schedule system which provide functions of personnel data management, national holiday management, holiday shift management, Automatic scheduling, scheduling demand management, scheduling statistics and schedule output. In the scheduling system interface, we make the system as simple as possible. In the user-side system, we develop App for users. Nurses or related staff can use the App directly to send the data by smart phone. In the core of the algorithm, we cooperate with the characteristics of the case, in line with the hospital policy, staff preferences, government regulations and so on under the premise of fair and independent goals.

**Keywords:** Schedule, App



## **決定 UV LED 陣列系統的殺菌條件**

Inactivation of aerosolized bacteria by UV LED system: effect of environment conditions on inactivation.

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醫院環境是病原微生物傳播的主要來源，而紫外線殺菌射是滅活空氣中微生物的有效方法。紫外線發光二極管（UV LED）具有以下優點：不含有毒的汞、設備簡單、靈活應用、不需預熱時間、耐用，在特定波長下發出單色光，多種波長，可脈衝照明，以及在低溫下保持較高活性的能力。經由UV-C紫外線照射後，在微生物之DNA中形成嘧啶二聚體，被認為是滅活細菌，病毒，原生動物，真菌，酵母和藻類微生物的最有效的消毒方式。在前期計畫中，已經完成紫外光脈波型式、照射細菌時間與距離、及照射細菌種類，其中包括具有抗藥性與否細菌與細胞壁厚薄不同的菌種。利用計畫所設計之高功率陣列型UV LED系統裝於自走車，運用於環境殺菌，並可對環境滅菌清潔，自走車同時裝配有電壓、電流、溫度及濕度等檢測器，以收集各項數據並運用環境監測系統，了解UV LED紫外線環境殺菌之條件，電壓、電流的感測可了解自走車的運作狀況，溫度、濕度的感測可了解環境的狀況，即時數據及曲線圖可做分析研究，此自走車具有運用在醫院、學校、廠房等之環境殺菌及數據收集之潛力。

**關鍵詞：**紫外線、空氣殺菌、微生物

The hospital environment is a source of pathogen transmission. Ultraviolet germicidal irradiation is an effective method to inactivate airborne microorganisms. Ultraviolet light-emitting diodes (UV LEDs) present several advantages, including the lack of toxic mercury, device conciseness and flexible designs, zero warm-up time, high solidity, monochromatic light emission at specific wavelength, wavelength diversity, possibility of pulsed illumination, and the capability of maintaining relatively high activity at cold temperatures. UV-C light is considered to be the most effective disinfectant region of the UV spectrum for inactivating microorganisms, such as bacteria, viruses, protozoa, fungi, yeasts, and algae, by the formation of pyrimidine dimer in the DNA. In the last project, the Researchers had designed three aims to optimize the period of UV pulse wave、exposing time and distance between irradiation source and bacteria, and to determine which kinds of bacteria, including gram-positive (thick cell wall) or negative bacteria (thin cell wall) and bacteria with antibiotic resistance, are more vulnerable to the UV-LED device. In the previous project, the pulse wave pattern of ultraviolet light, the time and distance of irradiating bacteria, and the types of irradiated bacteria have been studied, including whether they are resistant to drugs or not and those with different cell wall thicknesses. The high-power array UV- LED system designed by this project is installed on the self- driving vehicle, used for environmental

sterilization, and can sterilize and clean the environment. The self-driving vehicle is also equipped with detectors such as voltage, current, temperature and humidity to collect various data and use the environmental monitoring system to understand the conditions of UV-LED ultraviolet environmental sterilization. The sensing of voltage and current can understand the operation status of the vehicle, the sensing of temperature and humidity can understand the situation of the environment, and the real-time data and graphs can be analyzed and studied. This vehicle has the potential to be used for environmental sterilization and data collection in hospitals, schools, factories, etc.

**Keywords :** UV-LED 、 air disinfection 、 microorganism.

**UV LED 小型陣列系統之立體弧度角功率之分析**

Analysis of stereoscopic radian angle power of UV LED small array systems

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紫外光發光二極體（簡稱 UV LED）屬短波長的不可見光，波長範圍愈短，能量愈高，因具有較高的光子能量，可推動更高的能量化學作用，達到破壞強化學鍵的效果。依據 ISO 21348 的定義，電磁波波長範圍在 100 nm 至 400 nm 稱為紫外光，可分為：紫外線 A(UVA:315nm~400nm)、紫外線 B (UVB:280nm~315nm)、紫外線 C (UVC:100nm~280nm)等三類，其中以 UVC 的能量最強。

本研究是以 UVC LED (275nm)做為實驗的量測元件，UVC LED 普遍運用在表面、空氣和水這三部份需高功率的滅菌處理與消毒。針對 UV LED 元件的重要規格參數，如 Solid Angle、Radiant Flux、Peak 之元件光學與電性特性之推導，並搭配兩種不同的系統：ACC 與 AEC，在 LED 的照射距離、峰值、脈衝調變、電流、流速等進行實驗量測，以理論與實際值來探討輻射功率與立體弧度角的關係。

**關鍵詞：**紫外光發光二極體消毒系統、立體弧度

Ultraviolet light emitting diodes (UV LEDs for short) are short-wavelength invisible light. The wider the wavelength range, the higher it is. Because of its short photon energy, it can increase the energy chemistry and achieve the effect of destroying strong chemistry. According to the definition of ISO 21348, the electromagnetic wave range is within the wavelength range of 100nm to 400nm, which can be divided into: Nepal A(UVA: 315nm~400nm), North Korea B (UVB: 280nm~315nm), Berlin C (UVC: 100nm~280nm) Among the three categories, UVC has the strongest energy.

This paper uses UVC (275nm) as the experimental measurement. UVC LEDs are widely used in the treatment and disinfection of three types of LEDs that require high power: surface, air and water. For the important parameters of UV LED components, such as solid Angle, Radiant Flux, Peak components optical and electrical push, and there are two matching systems: ACCAEC, in the distance of the LED, wide range, modulation, current and other experiments Measure and discuss the relationship between radiant power and solid radian angle with theoretical and actual values.

**Keywords :** Ultraviolet light-emitting diodes, stereoscopic arc angle

**開發以計畫 AIoT 為基礎的大數據蒐集系統**

Development of Big Data Collection System Based on Architecture of AIoT Approach

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台灣已逐步進入老齡化社會。隨著最近又醫務人員的短缺，出現了許多經濟和社會問題。如何將通信技術和智慧生活科技應用於長者的照顧服務和醫療殺菌成為一個非常重要的問題。如果我們能夠整合智慧生活科技、滅菌系統和滅菌條件，提出以物聯網為基礎的智慧滅菌創新思想，對於改善醫療品質會有很大幫助。

本計畫是總計畫“在不同環境因素下高功率陣列型 UV LED 系統設計及應用研究”的子計畫二。我們開發智慧滅菌系統在不同環境參數下的效果分析，並將子計畫一“UV LED 小型陣列系統之立體弧度角功率之分析”、本子計畫二以及子計畫三“決定 UV LED 陣列系統的殺菌條件”整合在一起。本子計畫二提出了一種以物聯網為基礎的智慧殺菌環境大數據資料搜集平台的創新理念，並將其與智慧消毒設備一起實施，以提供更好的醫療服務，從而提高醫療服務的效率和質量。

在這個子計畫中，我們建置物聯網環境數據資料蒐集平台軟硬體架構。平台可接收匯整來自感測器的資料，做為大數據的資料來源。平台可實際應用於醫院，監控場域的環境數據，幫助管理人員掌控場域。透過平台可以讓環境數據資料視覺化，管理人員只要透過瀏覽器就可以在網站上看到視覺化資料，了解場域的環境數據，減輕人員的場域管理的負擔。

Taiwan has gradually entered the aging society. With the recent shortage of medical personnel comes the economic and social issue. How can the communications technology and intellectual technology be applied in care services and medical sterilization becomes a very important issue. If we can integrate the smart technology, sterilization system, and sterilization conditions, and propose innovative ideas of smart sterilization based on the Internet of Things. It will be greatly helpful in improving medical quality.

This project is a sub-project of the integrated project " Design and application of high-power array UV LED systems under different environmental factors ". This project collects environmental Big Data by using sensing signals, and uses a UV LED sterilization system to perform sterilization procedures through the selection and setting of sterilization mode, all of these operations are based on the Internet of Things.

In this project, we build the hardware and software architecture of the IoT environment data collection platform. The platform can receive and aggregate data from sensors as a data source for big data. The platform can be practically used in hospitals to monitor environmental data in the field and help managers control the field. Through the platform, environmental data can be visualized, and managers can see the visual data on the website through a browser, reducing the burden of field management for personnel.

#### 不同基因亞型乳癌存活者之復發狀態、創傷後成長、照護需求及生活品質：病歷回溯暨橫斷性研究

Recurrent status, post-traumatic growth, care needs and quality of life in different subtypes of breast cancer survivors: A retrospective chart review and cross-sectional study

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乳癌基因亞型為復發之重要預測變項，三陰性易復發、轉移且預後不佳。乳癌復發，從疾病進展到治療所致的心理、情緒反應讓個案的因應能力、對健康的感受與生活品質變差，而生活品質為復發乳癌存活狀態之重要預後因子。本研究之目的在探討乳癌存活者 10 年內之復發狀態、創傷後成長、照護需求及生活品質之現況。並進一步探討不同基因亞型乳癌存活者 10 年內於研究變項之差異。

本研究為病歷回溯合併橫斷性設計，立意取樣 450 名 2021 年 1 月到 12 月於中部某醫學中心門診就診 2011 年 1 月~2020 年 12 月初診斷 0~III 期乳癌、年滿 20 歲以上之成年女性。排除診斷時即為轉移癌、有其他癌症或心理疾患者。研究變項包括人口學、臨床相關變項、乳癌基因亞型、10 年內復發狀態、創傷後成長、照護需求及生活品質。研究工具為創傷後成長量表、支持照護需求量表修改中文版 34 題及癌症治療功能性評估- 乳癌症狀指標。統計方法以平均值、標準差、頻率及百分比描述樣本及研究變項之分布；並以 ANOVA 及 logistic regression 檢定研究假設。

本研究結果整體復發率 9.1%，以 ER-，Her2+ 組為最高且達顯著 (OR=2.29, p=0.037)、三陰性組次之但未達顯著 (OR=1.396, p=0.513)、ER+，Her2- 組復發之機率顯著較低 (OR=0.506, p=0.047)。ER+，Her2- 組的生活品質及生活品質滿意度顯著優於 ER+，Her2+ 組；症狀嚴重度、害怕惡化及創傷後成長各組間之得分皆未達顯著差異。照護需求的檢定中，僅其次量表日常生活活動達顯著差異，ER+，Her2- 組顯著低於 ER-，Her2+ 組，即 ER-，Her2+ 組未滿足之需求顯著較高。

**關鍵字：**不同基因亞型乳癌、三陰性乳癌、復發狀態、創傷後成長、照護需求、未被滿足之需求、生活品質

The risk of breast cancer mortality is varied among different subtypes of breast cancer survivors and the gene-subtype is proposed to be one of the significant prognostic factors of breast cancer mortality. Moreover, the highest risk gene-subtype of breast cancer recurrence, metastasis and mortality is triple negative breast cancer. Breast cancer recurrence, from diagnosis to disease progress, causes survivor's distress on physical and psychological domains of health, as well as hampers their quality of life. Quality of life is the essential factor for survivors to fight for the recurrence status. The aims of this study are to examine the phenomenon of recurrent status, post-traumatic growth, care needs, unmet needs, and quality

of life in different subtypes of breast cancer survivors diagnosed in the past ten years and to explore the differences on recurrent status, post-traumatic growth, care needs, unmet needs, and quality of life between different subtypes of breast cancer survivors.

This is a retrospective chart review and cross-sectional questionnaire study utilized a purposive sampling to enroll 450 stage 0-III breast cancer survivors newly diagnosed between 2011 and 2020. Participants have to be aged at least 20 years and follow-up at the outpatient department between January and December 2020 in a medical center located in the middle Taiwan. Those are with metastasis at the first diagnosed, or having a second cancer or mental illness will be excluded from this study. Research variables include demographics, medical information, gene-subtypes, post-traumatic growth, care needs, unmet needs, and quality of life. Research instruments consist of Posttraumatic Growth Inventory, Supportive Care Needs Survey- Short Form version 3, and Functional Assessment of Cancer Therapy- Breast Symptom Index. Descriptive analysis (mean, standard deviation, frequency and percentage), ANOVA and logistic regression are performed based on the study hypotheses.

Results of this study found the recurrent rate was 9.1%. The ER-, Her2+ subgroup has a significantly highest recurrent rate (OR=2.29, p=0.037) compared to the others, while the triple negative subgroup was in the second but not significant (OR=1.396, p=0.513). The ER+, Her2- subgroup has a significant lowest recurrent rate (OR=0.506, p=0.047). The quality of life and life satisfaction in the ER+, Her2- subgroup were significantly better than they were in the ER+, Her2+ subgroup. No significant differences were detected among subgroups in symptom, fear of progression and post-traumatic growth. For care needs, the only significance was found on the activities of living subscale between ER+, Her2-subgroup and ER-, Her2+ subgroup.

**Keywords:** different subtypes of breast cancer, triple negative breast cancer, recurrent status, post-traumatic growth, care needs, unmet needs, quality of life

## 探討台灣本土大蟬花Wu-BFP-14的生物安全性與保護肝臟功效機制

Explore the Biosafety of Taiwan Cordyceps cicadae Wu-BFP-14 and Its Mechanisms of Protecting Liver

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大蟬花(*Cordyceps cicadae*)是寄生於蟬科幼蟲的真菌，被認為與冬蟲夏草(*Ophiocordyceps sinensis*)有相似功效。乙醯胺酚(Acetaminophen, AP)為廣泛使用的鎮痛解熱藥物，但過量使用時會導致急性肝損傷(Acute liver injury, ALI)，甚至導致死亡。本研究探討人工篩選與培養的大蟬花 Wu-BFP-14 子實體(Fruiting body, FB)與菌絲體(Mycelium, MC)的生物安全性，以及對 AP 過量引起實驗小鼠 ALI 的保護作用與可能機制。首先利用急毒性試驗分別灌餵實驗小鼠 1 g/kg 或 5 g/kg 劑量的 FB 或 MC，每天觀察實驗小鼠並在 14 天後犧牲。結果顯示餵食 1 g/kg 或 5 g/kg 劑量 FB 或 MC 的實驗小鼠之血清肝、腎功能指數皆與灌餵相同體積的磷酸鹽緩生理食鹽水(Phosphate buffered saline, PBS)對照組小鼠沒有顯著差異，而在肝、腎病理切片染色結果也沒出現顯著的細胞損傷，顯示人工培養的大蟬花 Wu-BFP-14 之 FB 和 MC 管餵到 5 g/kg 都對實驗小鼠沒有明顯的肝、腎毒性。在護肝實驗部分，先分別管餵 250 和 500 mg/kg FB 或 MC，1.5 小時後以 AP 誘導實驗小鼠產生 ALI。血清肝臟功能指標與肝臟病理切片染色結果顯示 MC 有顯著護肝功效並具有劑量效應，而 FB 沒有顯著護肝功效。將 MC 以純水(MCW)或以 95% 乙醇(MCE)進行萃取所得萃取物，再分別連續三天管餵實驗小鼠 62.5、125 及 250 mg/kg 劑量，再以 AP 誘導 ALI，發現 MCW62.5 及 MCW125 組皆有效減緩 AP 誘導的血清肝臟功能指數上升與肝細胞損傷，但 MCW250 組和不同劑量的 MCE 組則無顯著的護肝效果。進一步研究 MCW62.5 及 MCW125 組護肝的機制，發現主要是透過提升肝臟中穀胱甘肽(Glutathione)含量、增加穀胱甘肽過氧化物酶(Glutathione peroxidase)活性及降低脂質過氧化，並透過抑制主要發炎因子表現量，降低肝臟中的細胞凋亡，來達到保護肝臟細胞效果。因此，大蟬花菌絲體純水萃取物可能開發成護肝的保健產品。

**關鍵字：**台灣本土大蟬花，發酵菌絲體，固態培養子實體，乙醯胺酚過量，急性肝損傷小鼠模式，致死性肝衰竭小鼠模式，動物安全性。

*Cordyceps cicadae* is a fungus that parasitizes the larvae of the family Cicadae and is thought to have similar efficacy to *Ophiocordyceps sinensis*. Acetaminophen (AP) is a widely used analgesic and antipyretic drug, but excessive use can lead to acute liver injury (ALI) and even death. This study investigated the biosafety of artificially screened and cultured *C.*

*cicadae* Wu-BFP-14 fruiting body (FB) and mycelium (MC), and their hepatoprotective effects and possible mechanism(s) on ALI in laboratory mice caused by excessive AP. First, laboratory mice were fed with FB or MC at a dose of 1 g/kg or 5 g/kg in an acute toxicity test. These laboratory mice were observed everyday and sacrificed after 14 days. The results showed that the serum indexes of liver and kidney in mice fed with 1 g/kg or 5 g/kg of FB or MC were the same as those mice in the control group fed with the same volume of phosphate buffered saline (PBS). There was also no significant difference in cells of sections from liver and kidney. In brief, there is no obvious liver and kidney toxicity in mice for feeding with 1 g/kg or 5 g/kg of FB or MC. In liver protection experiment, firstly, 250 and 500 mg/kg FB and MC were fed in mice, respectively. After 1.5 hours, mice were induced ALI by intraperitoneal injection of AP. The results of serum liver indexes and liver sections showed that MC had significant liver protection effect in a dosage-dependent manner, while FB had no significant liver protection effect. MC was extracted with pure water (MCW) or with 95% ethanol (MCE), and then mice were fed with doses of 62.5, 125 and 250 mg/kg for three consecutive days, respectively. After 1 hours, ALI in mice was induced with AP injection. Mice in the MCW62.5 and MCW125 groups both effectively decreased the AP-induced increase in serum liver indexes and hepatocyte injury, but mice in the MCW250 group and the MCE groups had no significant liver protective effect. Furthermore, to study the mechanism(s) of liver protection in mice of the MCW62.5 and MCW125 groups, it was found that it is mainly through increasing the hepatic content of glutathione, increasing glutathione peroxidase activity, reducing lipid peroxidation, inhibiting the expression of major inflammatory factors, and reducing apoptosis in the liver. Therefore, the pure water extract of the mycelium of *C. cicadae* Wu-BFP-14 may be developed as healthy products for protecting liver.

**Keywords:** Taiwan local *Cordyceps cicadae* Wu-BFP-14, fermented mycelia, solid culture fruiting bodies, acetaminophen overdose, mouse model of acute liver injury, mouse model of acute liver failure, animal safety



## TCVGH- DYU1108303

### 探討蛹蟲草和蟬花應用於蟑螂過敏原誘發異位型皮膚炎細胞模式之治療機轉

Investigate anti-atopic dermatitis effect of *Cordyceps militaris* and *Cordyceps Cicadae* through HaCaT model mediated by American cockroach allergens

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異位性皮膚炎是一個複雜的過敏性皮膚疾病，尚未完全了解，表皮屏障損毀和 Th2 免疫細胞反應失衡是其可能致病機轉。蟑螂過敏原被認為可能影響異位性皮膚炎病程進展的因素。

本研究目標是進一步探討 Per a 2 是否透過影響 Erk1/2、P38、JNK 等訊息傳遞路誘導細胞激素和趨化因子的表現，以蛹蟲草和蟬花來探討是否透過抑制訊息傳遞路徑來抑制 Per a 2 誘導細胞激素和趨化因子產生。

我們的結果發現蟑螂過敏原 Per a 2 會誘發 IL-8、GM-CSF 和 CCL-20，Per a 2 作用與 Erk1/2、P38、JNK 訊息傳遞路徑有關。後續結果發現蛹蟲草抑制 p-Erk 訊息傳遞路徑來抑制 IL-8、GM-CSF、CCL-20，蟬花抑制效果沒有顯著差異。期望我們的研究結果可作為異位性皮膚炎的新的預防或治療策略。

**關鍵詞：**異位性皮膚炎、蛹蟲草、蟬花、美國蟑螂過敏原、細胞激素和趨化因子

Atopic dermatitis (AD) is a complex inflammatory skin disease that is not fully understood. Epidermal barrier disruptions and Th2 immune response suppressions are thought to play major roles in the pathogenesis of the disease. American cockroach allergens may influence development of atopic dermatitis.

The aim of this study was to investigate whether the major American cockroach allergen Per a 2 influence on the expression of cytokines and chemokines through extracellular signal regulatory kinase, jun N-terminal kinase or P38 mitogen-activated protein kinase, and whether *Cordyceps militaris* and *Cordyceps Cicadae* influence on the expression of cytokines and chemokines mediated by Per a 2 through signaling pathway.

Our data indicated the major American cockroach allergens Per a 2 could induce the overexpression of mRNA in IL-8, GM-CSF, and CCL-20 which may through Erk1/2, P38, and JNK pathway.

We find that *Cordyceps militaris* could inhibit expression of IL-8, GM-CSF, and CCL-20 which also through p-Erk pathway, but *Cordyceps Cicadae* could not. We hope these results which probably will open the way to new preventive or therapeutic strategies for atopic dermatitis.

**Keywords:** Atopic dermatitis, *Cordyceps militaris*, *Cordyceps Cicadae*, American cockroach allergens, cytokines and chemokines.

## 榮譽計畫

TCVGH-NCNU1107901

### 內分泌訊息調節嗅覺感覺神經元的突觸發生與功能並影響雄果蠅同性間求偶行為的發生

Synaptic organization and function of the *Drosophila* olfactory sensory neurons by endocrine signaling regulation in male-male courtship inhibition

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動物為了維持生理的恆定有賴於內分泌系統和神經系統來共同運作，證據顯示當 *Drosophila melanogaster* 的 *wide awake* (即 *wake*；生合成 WAKE) 在胰島素生成細胞中的表現缺乏，將影響該細胞 GABA<sub>A</sub> receptor (Resistance to dieldrin; Rdl) 的功能而促進類胰島素過度的分泌而促使咽側線合成 juvenile hormone 導致 20-hydroxyecdysone (20E) 的水平降低，其影響包括接受雄性特有性費洛蒙 11-cis-vaccenyl acetate (cVA) 的 Or67d 嗅覺感覺神經元 (olfactory sensory neurons; OSNs) 因 20E 啟動的蛻皮激素訊號 (ecdysteroid signaling) 的減弱，導致該細胞與下游投射細胞 (projection neurons; PNs) 的連結關係減少並使該神經元對 cVA 的感受能力明顯降低，這是內分泌神經網路失衡影響特定神經細胞終致發生非常軌的動物行為反應，此例證是由數個分子調節機制在生物體內的漫長旅程，長距離的相互影響整合了神經網路/內分泌/基因表現與動物行為間的密切關係。

The nervous and endocrine systems coordinate with each other to closely influence physiological and behavioural responses in animals. This study demonstrates that WAKE (encoded by *wide awake*, also known as *wake*) modulating the GABA<sub>A</sub> receptor Resistance to Dieldrin, in insulin-producing cells of adult male *Drosophila melanogaster*, maintains its levels and localisation from the plasma membrane. The sustainability of GABA sensitivity in insulin-producing cells may serve to precisely control the secretion of insulin-like peptides. Once insulin/insulin-like growth factor signalling continues, it directly elicits juvenile hormone biosynthesis in the corpus allatum, which in turn *leads to* considerable decrease in 20-hydroxyecdysone levels. Further, a reduction in ecdysone signalling substantially lowers the perception of the male-specific sex pheromone 11-cis-vaccenyl acetate by odorant receptor 67d olfactory neurons. These findings may explain why *wake* mutation prompts significant male-male courtship in *D. melanogaster*. This effect is characterized by a long course involving multiple molecular interactions, wherein imbalances in intricate neuro-endocrine networks affect specific nerve cells, which ultimately result in unconventional behavioural responses.

**石墨烯/奈米碳管/PDMS皮膚貼附性導電高分子複合材製作及生理監控應用**

The fabrication and physiological monitoring application of graphene/carbon nanotube/PDMS skin-mountable conductive polymer composite

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皮膚貼附型(Skin-mountable)或穿戴型(Wearable)電子元件因為有其貼附人體特性及長期監控人體訊號的需求引起多方關注。本計畫目的是將石墨烯二維材料與一維螺旋狀奈米碳管共同參混到光固化聚二甲基矽氧烷(Polydimethylsiloxane, PDMS)中製作出具皮膚貼附性的導電高分子材料，未來嘗試將此材料用於軟性電子材料應用，並且能在高度拉伸下也能透過電性改變來監控生理機能。計畫研究成果成功將石墨稀及奈米碳管依不同比例參混到 PDMS 中並量測其機械性質及電阻率。預計之後會在 PDMS 上製作出指插電極並研究其在拉伸下的電性或生理反應，如流汗等。

**關鍵詞：**軟性電子材料，聚二甲基矽氧烷，石墨烯，奈米碳管

The proposal aims to fabricate skin-mountable and wearable electronic devices using polydimethylsiloxane (PDMS) as flexible substrate and 2D-graphene, 1D carbon nanotube doped PDMS as electrodes. At the beginning we will try to evaluate the conductivity of the mixture of graphene/carbon nanotube/PMMA thin film and later use the mixture to fabricate interdigitated electrode onto PDMS substrate and evaluate its electronic properties under strain. We have successfully fabricated graphene/carbon nanotube doped PDMS polymer composites (PCs) and measured their mechanical and electrical properties. Further studies will concentrate on using the flexible electronic device to monitor the physiological feature, such as sweat.

**Keywords:** flexible electronic materials, polydimethylsiloxane, graphene, carbon nanotube

## 高基氏體與修飾微管在aggresome形成時的角色分析

The role of Golgi complex and modified microtubules in aggresome formation

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蛋白質摺疊失誤是細胞內常見現象，然而過多的錯疊蛋白則會引發細胞毒性；細胞為解決此一問題，發展出幾項對治方案。proteasome 是分解錯疊蛋白的主要胞器。然而，當錯疊蛋白不正常堆高時，例如在老化細胞或癌細胞中，或是當 proteasome 失活，如被抑制劑 MG132 作用時，細胞會產生另一種胞器 aggresome 來應付此緊急狀況。aggresome 雖已被發現多年，然而其形成機制甚或組成結構仍不明朗。aggresome 分布於細胞中心處，幾乎與 centrosome 或 Golgi complex (GC) 重疊；aggresome 外緣分布有 intermediate filament 成員 Vimentin 外框，此可以圈禁被 HDAC6 捕獲並運送進來的泛素化(ubiquitination)錯疊蛋白。為了分析 aggresome 形成機制，本計畫發現，GC 會於處理 MG132 時碎裂；值得注意的是，這些 GC 碎片不會隨機或均勻分布於廣大的細胞質區域，而是緊緊貼著並環繞 aggresome。利用基因沉默技術或化學抑制劑來打散 GC，會促進 aggresome 生成；然而，當 GC 碎片過於細小時，反而會抑制 aggresome 產生。由於 GC、包括其碎片，皆具有製造 microtubule 的活性，且 GC 所衍生的微管，都是維修飾型態，亦即 detyrosinated tubulin (或稱 Glu-tubulin) 和 acetyl-tubulin，此兩種微管皆緊緊環繞在 aggresome 周遭。我們利用 shRNA 技術沉默了微管修飾酵素  $\alpha$  TAT1 或 CCP1，發現 aggresome 生成受到了抑制。這些發現表明，GC 必須在 aggresome 形成時碎裂，一來是空出更多空間好讓 aggresome 使用，二來是產生修飾型微管，以協助組成 aggresome。由於抑制  $\alpha$  TAT1 或 CCP1 表現時，能夠協同性地增強 MG132 細胞毒性，顯示干擾 aggresome 生成，會增強 proteasome 抑制劑 MG132 的細胞毒性，此將有助於提高以 proteasome 抑制為作用機制的抗癌藥物療效。

**關鍵詞：**高基氏體、aggresome、微管修飾

It is well documented that extensive accumulation of abnormally folded proteins is toxic to cells. Hence, cells develop mechanisms to clear those protein toxicants. Proteasome is responsible for clearing most of the misfolded proteins; however, when tremendous amount of proteins is not folded normally such as in aged or cancer cells, or when proteasome is impaired, for example by chemical inhibitor such as MG132, another subcellular structure, aggresome, is induced. Being an organelle, the structural detail of aggresome is not well resolved. It is only known that aggresome, forming at cell center almost overlapping with centrosome and Golgi complex (GC), is enclosed by Vimentin cage, which functions in quarantining the misfolded

proteins, which are bound and transported by the acetylase HDAC6. Sequentially, autophagosome and lysosome are recruited to clear the toxic garbage. To dig out the mechanisms by which aggresome is built, we found in the preliminary results of the study that GC is fragmented during aggresome formation. Intriguingly, those GC fragments are not randomly or evenly distributed throughout the cytoplasm; by contrast, the GC fragments are tightly connected to aggresome by residing at the periphery of aggresome. We adopted two strategies to examine whether GC fragmentation is crucial for aggresome formation by silencing a Golgi assembly factor GRASP55, or treating cells with a GC disrupting agent BFA. We found that aggresome formation was promoted when GC was broken into larger fragments, nevertheless, when GC was disassembled into smaller granules, aggresome formation was impaired. Since GC, including its fragments, is known able to nucleate microtubule, and we found the GC-derived acetyl-tubulin or Glu-tubulin displayed a cage-like structure enclosing aggresome, together raising a possibility that the GC fragments-produced modified tubulins would be crucial for aggresome formation. Indeed, reduction of acetyl- or Glu-tubulin by knocking down  $\alpha$ TAT1 or CCP1, two enzymes catalyzing the formation of the two modified tubulins, greatly inhibited aggresome formation. Lastly, reduction of each one of the two modified tubulins synergistically promoted MG132-induced cell mortality. All these findings prompt us to conclude that GC undergoes fragmentation during aggresome formation, and the GC fragments promote aggresome formation by producing a modified tubulins-enclosed cage around aggresome. Reduction of the level of modified tubulins is considered as a novel strategy to enhance proteasome inhibitor-elicited cell mortality during cancer therapy.

**Keywords:** Golgi complex, aggresome, tubulin modification

#### 奈米金粒子攜帶正丁烯基苯酞藥物載體影響人類惡性膠質瘤細胞之探討

Study of Nanogold-Based Carriers for the Drug Delivery of Butylidenephthalide into Human Brain Glioblastoma Cells

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本實驗使用物理製程奈米金粒子作為載體傳送藥物進入細胞，我們已經開發出通過物理方法合成了一種新的奈米金粒子載體，同時通過聚乙二醇和承載正丁烯基苯酞藥物代入人類惡性膠質瘤細胞，以評估藥物遞送能力的有效性。混合之奈米載體尺寸鑑定，使用動態光散射儀與掃描式電子顯微鏡測定奈米粒子的粒徑、並且使用紫外光分光光度計、傅立葉轉換紅外線光譜儀並且為了確認奈米粒子的表面官能基之鍵結特定與其特定吸收吸收波峰之表現。同時經由半致死劑量初步節測試正丁烯基苯酞是否能夠毒殺人類惡性腦癌細胞，再並且使用細胞存活率實驗測試奈米金載體包覆丁烯基苯對於人類腦瘤細胞有顯著之毒殺能力，以及評估對正常細胞（內皮細胞）是否不具有毒殺效果之副作用之現象。由結果中可以發現在擁有正丁烯基苯酞之組別有較佳的毒殺癌細胞能力呈現。同時亦將評估載體之生物相容性之分析：比較奈米金載體包覆丁烯基苯正常細胞與腦瘤細胞之生長效應、測定其抗氧化自由基能力與抑制巨噬細胞或活化之能力，作為來應用於人體之安全性使用考量參考指標。同時亦將評估載體之生物功能性之分析：確認奈米金載體包覆正丁烯基苯酞攜帶於人類惡性腦癌細胞定量分析之驗證、檢測正丁烯基苯酞是否能夠有效誘導腦瘤細胞產生凋亡機制以及是否影響細胞週期之變化，研究將同時使用 Annexin V-FITC/PI 雙染色驗證我們將胞之攝取能力與相關涉入作用機制之釐清，並且將同時使用流式細胞儀進行奈米金載體包覆正丁烯基苯酞同時處理人類惡性膠質瘤細胞與正常內皮細胞藉以更進一步評估其對於細胞凋亡之表現與測試。同時更進一步探討細胞凋亡蛋白之表現程度，研究將使用西方墨點法探討細胞凋亡蛋白質(caspase-3、Bcl-2、Bax、Cyclin D1 與 p21) 更進一步作為釐清奈米金載體包覆丁烯基苯確實具有誘導人類惡性腦癌細胞的細胞凋亡路徑探討蛋白之有效抑制效果。我們期望藉由聚乙二醇改質的奈米金粒子並且包覆正丁烯基苯酞，能夠有效增強對於人類惡性膠質瘤細胞之毒殺能力，期望此新穎奈米藥物載體可以做為新一代奈米標靶藥物之有效應用指標。

**關鍵詞：**奈米金粒子、正丁烯基苯酞、人類惡性腦癌細胞、細胞凋亡

Nanoparticles based carrier are gaining popularity in research to serve as drug delivery system in past decades. Among them, gold nanoparticles (AuNP) has attracted more attention for the intuitive characteristics: inertial, easy fabrication, and surface plasmon resonance effect.

In this study, we use physical nanogold particle (AuNP) as a carrier to deliver drugs into cells, and we have developed a new synthesis of nanogold particle carrier by physical methods, and by polyethylene glycol (PEG) to link n-butylidenephthalide (BP). To assess the effectiveness of drug delivery ability, we treat it into human malignant glioma cancer cells (DBTRG). To identify and characterization the size of AuNP-PEG-BP nanocarrier by using dynamic light scattering (DLS), UV-Visible Spectrophotometer and Fourier Transform Infrared Spectroscopy (FTIR) in order to double confirm the functional group bond of the surface of the nanoparticles. To evaluate the biocompatibility of AuNP-PEG-BP affecting safety issue for human bod we also compare both transform cells (DBTRG) and non-transform cells (bovine aortic endothelial cells, BAEC) (e.g. cell growth effect, anti-oxidant ability and macrophage activation inhibition test) of AuNP-PEG-BP nanocarrier.

Moreover, to explore the molecular mechanism of affecting cell behavior (cellular uptake effect and mechanism, cell toxicity ability, apoptosis effect and anti-migration effect) was also elucidate in this study. We are currently performing the in vitro experiments. It will take times for the execution of these in vitro experiments and further confirmed its potential for therapeutic of human malignant glioma cancer cells.

**Keywords:** nanogold particle, n-butylidenephthalide, human malignant glioma cancer cells, apoptosis

## 住院照護日誌對於病房家屬照護與醫病溝通的輔助價值

The value of Admission Diary in the communication among patient's families and medical professionals.

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**Purpose:**依據美國內科醫學委員會 (American Board of Internal Medicine, 簡稱 ABIM) 於 2012 年發起「choosing wisely」活動、109 年評鑑條文草案 2.1.3「向住院病人或家屬說明住院之必要性及診療計畫，並有措施協助及鼓勵其參與醫療照護之過程及決策」；與衛福部 109-110 年病安年度工作目標八：「鼓勵病人及其家屬參與病人安全工作」，醫療照護已朝向鼓勵病人家屬參與照護並建立確效的醫病溝通管道邁進。病人、醫療人員與病人家屬，在住院照護過程期間的互動、溝通與合作方式，影響著病人的病情發展、家庭功能和全人照護，近幾年因國際新冠肺炎(covid-19)疫情的肆虐，醫療院所對於訪視探病更加嚴謹，多數時期關閉加護病房探病亦或禁止人員進出病房。在減少甚至完全沒有會客次數的狀況下，要達到有效的醫病溝通、提升家屬參與照護過程，是值得探討的問題之一。

**Patients and Methods:**研究期間為 2020 年 08 月至 2021 年 04 月 20 日止共 9 個月，由醫療人員向家屬解釋研究之過程，取得家屬同意並簽署受試者同意書後，發予住院照護日誌乙本，該日誌內容主要包括三大部分，加護病房簡介和相關衛教 QR code、問題引導範例和每日提問與紀錄頁。日誌使用經驗問卷分為家屬和醫療人員兩種版本，問卷的編製主要是經由研究團隊成員討論擬訂，並經問卷專家參與之焦點團體會議共識編擬而成，藉以瞭解本工具對於溝通和資訊傳遞的效益。透過非隨機分派的介入性研究方法，探討加護病房病人之家屬使用住院照護日誌的經驗結果，分析統計逐字稿內容與家屬、醫療人員使用經驗問卷，以 SPSS 24.0 版統計軟體進行處理與分析，來探討年齡、不同加護病房在醫病溝通互動、訊息傳遞、家屬參與、照護知能和滿意度等之相關性。

**Results:**研究於本院第一加護病房、呼吸加護病房和外科加護病房執行，完成收案數共計家屬 106 位和醫療人員 30 位，家屬性別男女比例為 1:1.65。家屬執筆之日誌紀錄筆數總共有 796 筆，其中病情相關問題(我想問的問題是) 300 筆、醫師交代說明的事 293 筆和對於醫療團隊的提醒(我想跟醫護人員交代的事) 203 筆。有 7 成以上的家屬撰寫至第 5 日，日誌完成至第 10 日共有 14 位。使用經驗問卷中，家屬的整體平均分數為 3.37 分(非常同意為 4 分)，最高分項目為題項 1.幫助我與家人之間的溝通(3.46)和題項 2.幫助我與家人取得醫療上的共識(3.46)；最低分則為題項 9.我想以手機或平板等 3C 裝置使用住院照護日誌(3.19)。醫療人員的問卷結果整體平均分數為 3.12 分(非常同意為 4 分)，最高分項目為題項 3.可以幫助家屬辨識想詢問的問題(跟醫師講事情更清楚明確) (3.23)；最低為題項 7.可以降低照顧家屬的焦慮程度(3.19)。

**Conclusions:**本研究為國內首創且與國外醫療人員執筆的加護病房日誌有很大的不同，獲得 85% 以上的家屬同意在溝通、交班、掌握資訊、降低焦慮和心理支持有幫助；醫療人



員雖持同意想法但無形中也增加了醫療人員的工作量。住院照護日誌對於醫病溝通、病人參與、健康適能和照顧者焦慮程度有一定的潛在臨床價值，由歸納出的質性經驗文本支持量化的問卷結果，確實可達到加護病房團隊與家屬的溝通、減少醫療糾紛並提高整體的滿意度。

**Key Words:** 加護病房(intensive care)、照護日誌(patient diaries)、家屬參與(family engagement)、醫病溝通(medical-patient communication)、質性研究(Qualitative research)

**Purpose:** According to the "choosing wisely" campaign launched by the American Board of ABIM in 2012, article 2.1.3 of the 109-Hospital–Accreditation, and 109-110 Hospital Patient Safety Annual Goals No. 8 published by the Ministry of Health and Welfare, healthcare has moved towards encouraging family members of patients to be involved in care as well as Establishing effective communication channels between medical staff and patients. The way patients and their families interacted, communicated and cooperated with medical staff during hospitalization affected the development of the disease and family relationship. In recent years, due to the ravages of the international epidemic(covid-19), medical institutions have become more strict about visiting patients. Most of the time, the intensive care unit is closed for visiting patients or people are prohibited from the ward. Under this circumstance, how to achieve effective communication between medical staff and patients is worth exploring.

**Patients and Methods:** The study was done from August 2020 to April 20, 2021.in the ICU of Taichung Veterans General Hospital. The medical staff explained the research process to the family members, and then delivered a hospital care diary. The content of it included three parts: the introduction of the intensive care unit, the relevant health education QR code, and the daily question and record page. In order to estimated the benefits of the diary, family members and medical staff needed to fill the experience questionnaire individually after diaries were completed. The questionnaire was divided into two versions: family members and medical personnel. We explored the outcomes of using diaries through a nonrandomized, interventional approach, statistical software of SPSS version 24.0 was used for processing and analysis.

**Results:** The study was carried out in the First ICU, Respiratory ICU and Surgical ICU. A total of 106 family members and 30 medical staff were accepted. There were a total of 796 log records written by family members, of which 300 were related to illness, 293 were doctor's explanations and 203 were the reminder to the medical team. In the experience questionnaire, the overall average score of family members was 3.37/4, and most family members affirmed that the diary did helped the communication (3.46). The overall average score of the medical staff's questionnaire was 3.12/4, and most medical professionals agreed that the diary could help family members identify the questions they want to ask(3.23).

**Conclusions:**

This study was the first of its kind in Taiwan and was very different from the ICU diary

written by foreign medical staff.

More than 85% of the family members agreed that it was helpful for communication, mastering information, and reducing anxiety; although medical staff agreed as well. However, using diaries also increased the workload of medical staff. The ICU diary had a certain potential clinical value for doctor-patient communication, patient engagement, health fitness, and caregiver anxiety. It could achieve communication between the ICU team and family members as well as improve overall satisfaction, through the quantitative questionnaire results supported by summarized qualitative empirical text.

**Keywords:** intensive care · patient diaries · family engagement · medical-patient communication · Qualitative research

**創意桌遊與特殊教育需求學生的人際關係及情緒健康**

Creative board games and the interpersonal relationship and emotional health of students with special educational needs

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本研究藉由系統性文獻回顧 2006 年 5 月 31 日至 2021 年 12 月 31 日前發表於電子資料庫之中、英文文獻，整合國、內外社交技巧訓練相關研究，了解創意桌遊等社交技巧訓練對社區思覺失調症特殊教育需求學生人際關係及情緒健康之成效，期望提供臨床精神復健醫療人員參考，助益我國精神照護服務的推動。

**關鍵詞：**特殊教育需求學生、創意社交技巧訓練、系統性文獻回顧。

Through a systematic review, the Chinese and English literatures published in the electronic database from May 31, 2006 to December 31, 2021, integrated domestic and foreign research related to social skills training, and learned about creative board games and other social skills training. Regarding the effect of interpersonal relationships and emotional health of schizophrenia students with special educational needs in the community, it is hoped to provide reference for clinical mental rehabilitation medical personnel, and to help the promotion of mental care services in my country.

**Keywords:** students with special educational needs, creative social skills training, systematic review.

## TCVGH-CTUST1107704

### 順鉑與得舒緩雙抗藥性細胞透過外泌體內微小分子核糖核酸轉介抗性予無抗性母細胞

Cisplatin-erlotinib double-resistance cells transfer the resistance to non-resistance parental lung cancer cells via exosomal microRNAs

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外泌體及其內 miRNA 群在致癌作用與癌症行為之關鍵角色是當紅未解的研究重心之一。我們假設具順鉑-得舒緩雙重抗藥性肺癌細胞所分泌之外泌體中的 miRNA 可能有助於其親代非抗藥肺癌細胞株獲得抗藥性徵。方法：我們已經成功建立了雙重抗藥肺癌細胞，並以它們產生的外泌體處理親代 NCI-H1975 和 A549 肺癌細胞。我們的研究亮點是將親代肺癌細胞以兩次雙重抗藥肺癌細胞分泌外泌體進行處理後，其細胞有明顯的增殖。接著，我們以 miRNA 微陣列比較控制組和外泌體處理細胞之間的差異。我們把這些表現量上升的 miRNA 逐一轉染到親代細胞中，並分析其對順鉑和得舒緩靈敏度之效用。此研究將有助揭櫫 miRNA 在抗藥性肺癌治療中的作用。結果：從雙重抗藥的肺癌細胞中分離的外泌體可明顯提高了親代肺癌細胞 A549 和 NCI-H1975 細胞的增殖。miRNA 微陣列分析顯示，與親代細胞相比，具抗藥性 A549 細胞中的 miRNA 564 和 miRNA658 表現顯著上升。總結：雙重抗藥肺癌細胞產生之外泌體 miRNA 可能誘導其親代癌細胞獲取抗藥性。外泌體 miRNA 間的細胞訊遞未來可做為對抗肺癌治療抗藥性的新靶標。

**關鍵詞：**外泌體、順鉑、肺癌、雙重抗藥性肺癌細胞

Purpose: Exosomes and inside cargo microRNAs play a critical role in various carcinogenesis and cancer behaviors. We hypothesize that microRNAs in exosomes secreted from cisplatin-erlotinib double-resistant lung cancer cells might contribute to the resistant phenotypes in its parental non-resistant lung cancer cells. Methodology: We have successfully established the cisplatin-erlotinib double-resistant lung cancer cells and isolated the exosomes generated by them from the parental lung cancer cells NCI-H1975 and A549. The highlight finding is that the parental cells after the two repeated challenges with the exosomes collected from double-resistant cells, and these parental cells are evaluated for their cell proliferation after being treated with exosomes. Then the miRNA array is conducted for comparing the sham-treated and exosome-treated cells for differential expression. We transfected these up-regulated microRNAs one by one into the parental cells and analyze the effects on their sensitivity to cisplatin and erlotinib. Then we investigated the roles of miRNAs in therapeutic resistance of lung cancer. Results: Exosomes isolated from cisplatin-erlotinib double-resistant cells significantly increase the proliferation of parental A549 and NCI-H1975 cells after

double treatment. Interestingly, the miRNA array analysis shows that several miRNAs, such as miRNA 564 and miRNA658, are significantly upregulated in resistant A549 cells, compared with parental cells. In the future, we are going to examine the gain-of-function effects via transfecting miRNA 564 and miRNA658 into the parental A549 cells. Conclusion: Exosomal miRNAs derive from cisplatin-erlotinib double-resistant lung cancer cells induced drug resistance in their parental cancer cells. Cell-cell communications via exosomal microRNAs can serve as novel targets for the war against drug resistance in lung cancer therapy.

**Keywords:** Exosomes; cisplatin; lung cancer; double-resistant lung cancer cells

芳烴受體在小鼠糖尿病性視網膜病變中起保護作用

The aryl hydrocarbon receptor plays a protective role in diabetic retinopathy in mice

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越來越多的文獻報導證據顯示糖尿病導致視網膜病變 (DR) 的病理生理過程，然而保護途徑的作用受到的關注仍十分有限。轉錄因子芳烴受體 (AhR) 是生物體化學物質的重要傳感器，並以配體特異性，細胞類型特異性和不同生物細胞組織有其特異性方式整合複雜的轉錄程序。這項研究的目的是將進一步探討 AhR 作為 DR 中保護機制的潛在作用可行性。方法採用免疫組織化學方法檢測人類供體和小鼠眼中 AhR 的視網膜表達。在人類視網膜色素上皮細胞 (HRPEpiC) 和 ARPE-19，一種人類視網膜色素上皮細胞系中研究 AhR 調節對氧化壓力的影響。評價比較非糖尿病和鏈脲佐菌素誘導的糖尿病野生型小鼠和 AhR 基因敲除小鼠的多個 DR 終極目標與終點。結果顯示:AhR 在人和小鼠視網膜的視網膜色素上皮細胞中顯著表達。在培養的視網膜色素上皮細胞中，AhR 抑制作用顯著降低了抗氧化劑基因的表達，並加劇了叔丁基過氧化氫和過氧化氫誘導的氧化壓力反應。 AhR 活化劑大大增加了 AhR 目標基因的表達，並抑制了氧化劑誘導的活性氧。糖尿病小鼠表現出視網膜 AhR 活化激活作用。與野生型小鼠相比，AhR 基因敲除小鼠的糖尿病中超氧化物水平顯著增加。與野生型小鼠相比，糖尿病 AhR 基因敲除小鼠的視網膜穀胱甘肽減少更多，TNF- $\alpha$  蛋白增加。在糖尿病中，AhR 基因敲除小鼠表現出較早的血-視網膜屏障功能障礙和神經元功能障礙的發作。結論/解釋這些初步結果證實，AhR 是調節 DR 進程的重要保護因子，初步顯示增強 AhR 途徑是一種潛在的治療策略。

**Aims/hypothesis** Emerging evidence indicate the pathophysiological processes contributing to diabetic retinopathy (DR), the role of protective pathways has received less attention. The transcription factor aryl hydrocarbon receptor (AhR) is an important sensor of xenobiotic chemicals and integrates complex transcriptional programmes in a ligand-specific, cell-type-specific and context-specific manner. The objective of this study was to explore the potential role of AhR as a protective mechanism in DR.

**Methods** Retinal expression of AhR was investigated in human donor and mouse eyes by immunohistochemistry. The effect of AhR modulation on oxidative stress was studied in the Human Retinal Pigment Epithelial Cells (HRPEpiC). and ARPE-19, a human retinal pigment epithelial cell line. Non-diabetic and streptozotocin-induced diabetic wild-type and AhR knockout mice were evaluated for multiple DR endpoints.

**Results** AhR was expressed prominently in retinal pigment epithelial cell in both human and

mouse retinas. In cultured retinal pigment epithelial cells, AhR inhibition significantly decreased antioxidant gene expression and exacerbated tert -butyl hydroperoxide- and hydrogen peroxide-induced oxidative stress. AhR activation strongly increased AhR target gene expression and suppressed oxidant-induced reactive oxygen species. Diabetic mice exhibited retinal AhR activation, indicated by nuclear translocation. Superoxide levels were significantly increased by diabetes in AhR knockout mice as compared with wild-type mice. Diabetic AhR knockout mice exhibited a reduction in retinal glutathione and an increase in TNF- $\alpha$  protein compared with wild-type mice. AhR knockout mice exhibited early onset of blood–retina barrier dysfunction and exacerbation of neuronal dysfunction in diabetes.

**Conclusions/interpretation** These results indicate that AhR is an important protective factor regulating the progression of DR and suggest enhancement of the AhR pathway as a potential therapeutic strategy.

## 建立模型系統探討抗葉酸免疫調節藥甲氨蝶呤與葉酸救援如何交互影響胞內代謝路徑之動態平衡

Establishment of model systems to investigate how antifolate DMARD methotrexate impact cellular metabolic kinetics

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背景：抗葉酸甲氨蝶呤 (methotrexate) 是治療人類類風濕性關節炎 (rheumatoid arthritis) 最常用的疾病抗風濕藥物。粒線體產生的甲酸鹽對於葉酸介導的單碳代謝至關重要。嚴謹動力學的研究對於研究甲氨蝶呤如何影響甲酸鹽穩態有很大的幫助。材料與方法：結合細胞模式與穩定同位素追蹤研究與氣相層析質譜平台，我們系統性地研究甲氨蝶呤如何干擾粒線體和細胞質甲酸鹽代謝分配。結果：進一步把細胞發現的結果與蔣老師研究室之動物模式實驗獲得的數據獲得的數據獲得的數據相互比對，發現甲氨蝶呤顯著降低細胞及小鼠肝臟和骨髓中透過粒線體生成的甲酸鹽所支援的脫氧胸苷酸新合成 (deoxythymidylate, TMP) 和甲硫氨酸 (methionine)，研究結果支持我們的假設，即甲氨蝶呤會耗盡線粒體單碳供應。亞葉酸 (folinate) 對於細胞和不同代謝系統路徑顯示出選擇性地拯救效應。針對單碳代謝路徑亞葉酸可有效逆轉甲氨蝶呤對於細胞脫氧胸苷酸新合成中來自粒線體甲酸依賴性單碳代謝之抑製作用，但卻無法改善人類肝源細胞中的甲硫氨酸之合成。亞葉酸無法完全恢復甲氨蝶呤對肝中線粒體甲酸鹽利用合成甲硫氨酸之抑制，表明臨床上若意圖用亞葉酸減緩甲氨蝶呤治療中對肝中甲硫氨酸代謝的療效效果有限。結論：在細胞模式中我們證明甲氨蝶呤會特異性地消耗粒線體單碳代謝的供應等新發現，除了肝臟轉甲基化之外，可以通過補充亞葉酸來改善甲氨蝶呤的甲酸鹽消耗。這些結果表明，臨床使用低劑量甲氨蝶呤可能透過線粒體甲酸鹽消耗來阻礙單碳代謝。低劑量甲氨蝶呤治療所造成的系統性和組織特異性甲酸鹽耗竭現象、以及補充亞葉酸鹽在改善甲酸鹽消耗的效益值得在臨床實踐中被仔細評估並提出解決策略。

**關鍵字：**抗葉酸免疫調節藥物;甲氨蝶呤;細胞模式;穩定同位素;代謝路徑追蹤

Objective. Antifolate methotrexate is the most common DMARD for treating human rheumatoid arthritis (RA). The mitochondrial-produced formate is essential for folate-mediated one carbon (1C) metabolism. The impacts of methotrexate on formate homeostasis is unknown. Combining cell models, stable isotopic tracer studies with GC/MS platforms, we systematically investigated how methotrexate interferes with the partitioning of mitochondrial and cytosolic formate metabolism. Methotrexate reduced de novo deoxythymidine (dTMP) and methionine biosyntheses from mitochondrial-derived formate in cell model, mouse liver and bone marrow, supporting our postulation that methotrexate



depletes mitochondrial 1C supply. Folate selectively rescued 1C metabolic pathways in a tissue-, cellular compartment-, and pathway- specific manner: folate effectively reversed the inhibition of mitochondrial formate-dependent 1C metabolism in mouse bone marrow (dTMP, methionine) and cell model (dTMP) but not methionine synthesis in liver/liver-derived cells. Compared to the animal models established in Chiang Lan, folate rescue failed to fully recover mitochondrial-formate utilization for methionine synthesis in liver/liver-derived cells, suggesting that the efficacy of clinical folate rescue in methotrexate therapy on hepatic methionine metabolism is poor. Our study greatly benefits patients taking methotrexate.

**Keywords :** antifolate immunomodulatory drugs; methotrexate; cell model; stable isotopic; metabolic pathway tracing

## **以細胞及動物模式探討 SGLT2 抑制劑 Dapagliflozin 減緩顯影劑誘發急性腎損傷**

Dapagliflozin, SGLT2 inhibitor, attenuates contrast-induced acute kidney injury in cell and animal model

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顯影劑是臨床醫療用於電腦斷層、心導管必須的藥品，但因為顯影劑造成的急性腎損傷(contrast-induced acute kidney injury, CIAKI)是台灣院內 AKI 的最主要原因之一，造成後續洗腎與死亡風險的顯著上升。目前仍無有效安全且廣泛應用的藥物可以預防。Dapagliflozin 是臨床上使用的 sodium glucose co-transporters 2 (SGLT2) inhibitor，可抑制腎小管對於糖份的再吸收，為新的糖尿病口服藥物。因其顯著對於病人心臟、腎臟的保護效果，目前已經被建議優先使用。近來 Dapagliflozin 在動物實驗中，藉由抗凋亡及抗氧化被證實對於急性腎損傷有保護的效果。但 Dapagliflozin 對於 CIAKI 是否有保化效果及其分子機制仍屬未知。在本計畫中，我們建立了使用顯影劑(iopamidol)處理人類腎近曲小管細胞(HK-2 cells)的細胞模式。證明再高葡萄糖環境中，Dapagliflozin 的濃度上升不會造成 HK-2 細胞的損傷，還能減少顯影劑對於腎小管細胞造成的細胞凋亡。而 Dapagliflozin 亦可誘發細胞自噬來抑制顯影劑對於腎小管細胞所誘導的細胞凋亡。利用糖尿病大鼠的顯影劑腎損傷模式，我們亦驗證 Dapagliflozin 對於顯影劑急性腎損傷的保護效果也存在於活體中，包括改善血清中尿素氮(blood urea nitrogen), 肌酸酐(creatinine)的濃度，維持正常腎臟組織結構，同時亦誘發細胞自噬及降低 NLRP3 發炎小體的活化。因此，我們推測 Dapagliflozin 在 CIAKI 可能扮演保護的角色。我們希望這項研究不僅能提供 Dapagliflozin 在腎臟病及糖尿病治療中的新視野，並且還為改善顯影劑腎損傷的臨床治療提供了新的策略。

**關鍵字：**顯影劑，急性腎損傷，dapagliflozin，細胞自噬，細胞凋亡

Contrast medium is necessary for hospital daily practice, but contrast-induced acute kidney injury (CIAKI) is the main cause of hospital acquired AKI, associated with great morbidity and mortality. Currently, there is no safe and effective therapy to prevent it. Dapagliflozin, the first approval sodium glucose co-transporters 2 (SGLT2) inhibitors with inhibition of sodium and glucose absorption in renal proximal tubules, is a promising new oral anti-diabetes agent with cardiovascular and kidney protection. Recently, dapagliflozin has been reported to attenuate acute kidney injury in ischemic reperfusion injury or sepsis AKI animal models through anti-apoptosis and anti- reactive oxygen species (ROS) effects.

However, the protective role of dapagliflozin in CIAKI is still unclear. In this study, we set up contrast medium iopamidol treated HK-2 cells (kidney proximal tubule epithelial cell line) as our cellular model. We demonstrated iopamidol could induce cell cytotoxicity and apoptosis of HK-2 cells. In contrast, dapagliflozin did not induce cytotoxicity but trigger autophagy in HK2 cells. In high glucose medium, pretreatment of dapagliflozin not only significantly prevented iopamidol-induced cytotoxicity and apoptosis in HK2 cells, but also further enhance strong autophagy. The dapagliflozin-induced autophagy may be protective and inhibit the iopamidol-induced apoptosis in HK2 cells. In the in vivo study, dapagliflozin treatment not only reduced the blood urea nitrogen and serum creatinine, but also inhibit the tissue damage in the STZ induced diabetic rat model with iopamidol-induced nephropathy. In the cell lysates of renal tissue, dapagliflozin treatment not only induced autophagy but also decreased the renal proximal tubule injury marker KIM-1 and NLRP3 inflammasome proteins. Taken together, we demonstrated that dapagliflozin may protect the kidney from CIAKI. We hope this study will not only provide a new vision of contrast induced AKI, but also offer an opportunity to expand the clinical role of SGLT2 inhibitors for diabetes and kidney diseases therapy.

**Keywords :** iopamidol, acute kidney injury, dapagliflozin, autophagy and apoptosis

## **L5 在抗磷脂抗體症候群致病機轉扮演的角色**

The role of L5 in the pathogenesis of antiphospholipid antibody syndrome

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### **背景**

L5 是低密度脂蛋白膽固醇中最易致動脈粥樣硬化的成分，最近的研究報導了全身性紅斑性狼瘡(SLE)患者的 L5 增加。抗磷脂抗體症候群 (APS) 是一種經常與 SLE 相關的自體免疫疾病。在這裡，我們旨在探討 SLE 和 APS 患者的心血管特徵和 L5 血漿濃度。

### **方法**

對於研究參與者，我們透過電泳和液相層析質譜分析了 L5 的血漿濃度。也透過超音波自動測量頸動脈內膜中層厚度 (IMT)。臂踝脈搏波速度 (baPWV) 也由血分析裝置測定。

### **結果**

我們招募了 25 名受試者，其中包括 4 名患有 APS 的 SLE 患者、5 名有抗磷脂抗體的 SLE 患者、10 名患有原發性血管性 APS 的患者、3 名產科 APS 患者和 3 名健康對照組。我們的結果發現 SLE 和 APS 患者的 L5 百分比和雙側頸動脈 IMT 增加。然而，baPWV 在各組受試者間沒有差異。

### **結論**

總結來說，SLE 和 APS 病患的 L5 百分比和頸動脈 IMT 增加。

**關鍵字:**抗磷脂抗體症候群; L5; 低密度脂蛋白; 紅斑性狼瘡

### **Background**

L5 is the most atherogenic fraction of low-density lipoprotein cholesterol (LDL-C). A recent study reported an increased L5 in patients with systemic lupus erythematosus (SLE). Antiphospholipid antibody syndrome (APS) is an autoimmune disease frequently associated with SLE. Here we aimed to explore the cardiovascular profile and plasma levels of L5 in patients with SLE and APS patients.

### **Methods**

For study participants, we analyzed plasma levels of L5 by electrophoresis and subsequent liquid chromatography. Carotid intima media thickness (IMT) was measured automatically by ultrasound. Brachial-ankle pulse wave velocity (baPWV) was also determined by the vascular profiling device.

### **Results**

We recruited 25 individuals, who were comprised of 4 SLE patients with APS, 5 SLE patients with aPL, 10 patients with primary vascular APS, 3 patients with obstetric APS, and 3 healthy controls. Our results demonstrated an increased L5 percentage and bilateral carotid IMT in

SLE and APS patients. However, baPWV did not differ between subgroups.

### **Conclusions**

In conclusion, L5 percentage and carotid IMT were increased in SLE and APS patients.

**Keywords :** antiphospholipid antibody syndrome; L5; low density lipoprotein; systemic lupus erythematosus

**基於深度學習之腎絲球影像資料增強與病理型態分類**

Deep learning-based data augmentation of glomerulus images with pathological morphology classification

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慢性腎臟病是台灣常見的疾病，為了提供更適宜的臨床照護，精確的原發疾病診斷相當必要，腎臟切片在提供精確的診斷上具有不可取代的地位，然而，由於腎臟切片的影像判讀十分耗費病理科醫師的時間與精力，當醫師經驗有限或工作負擔過重時，也有錯誤判讀的風險，因此透過電腦系統輔助診斷確有其重要性。於本計畫中，我們透過深度學習技術，進行腎臟病理影像中腎絲球偵測與正常及不同病理型態(含腎絲球硬化、增生、硬化加增生、與其它異常類)腎絲球之分類。計畫已收集 H&E 與 PAS 染色與不同放大倍數(200X, 400X)的切片影像進行實驗。在深度學習技術上，計畫提出新的深度學習架構，以提高網路對於腎絲球內部不同型態較小細節差異的辨識度，提高整體的腎絲球偵測能力，偵測效果優於 4 位參與實驗醫師。分類上，計畫提出階層式分類法。此法包含兩個階段。第一階段主要以深度學習架構執行腎絲球偵測，第二階段則負責腎絲球的正常與 4 種病理型態分類，提供醫師診斷參考。此外，計畫亦提出新的腎絲球類別資料增強方法。計畫提出利用循環生成對抗網路(CycleGAN)來達到資料增強的目的，提升了分類表現。

**關鍵字:**慢性腎臟病，腎臟病理，深度學習，電腦視覺、生成對抗網路

Chronic kidney disease (CKD) is a prevalent disease in Taiwan. Precise diagnosis of primary kidney disease is critical for the provision of appropriate clinical care. Renal biopsy is an important and unreplacable tool for the diagnosis. However, the interpretation of the result is quite time-consuming and labor-intensive. There is also a risk of misdiagnosis with an inexperienced or overloaded pathologist, which enhances the necessity of computer-assisted diagnosis system. This project has proposed a new method to detect glomeruli and classify normal and different types of pathological morphology, such as glomerulosclerosis and hypercellularity, of glomeruli in renal pathology images. This project has collected images from an all-optical microscope and the images were stained with H&E or PAS and photographed at 200 or 400 optical magnification. This paper has proposed a new deep learning method to improve glomerulus detection ability by distinguishing differences between the small components in different glomerulus morphologies. For the classification task, this

project has proposed a hierarchical classification structure consisting of two stages. The first stage detects glomeruli. The second stage is responsible for the classification of the glomeruli with five different morphologies. In addition, this project has proposed a data augmentation method for the classification problem by using the cycle-consistent generative adversarial network (CycleGAN). Data augmentation with the translated images has been shown to improve classification performance.

**Keywords** : chronic kidney disease, renal pathology, deep learning, computer vision, generative adversarial network.

**製備含親水鏈段或生物素之聚酯醯胺奈米微胞及其應用**

Prepare Functional Poly(ester amide)s Micelles Comprising Hydrophilic Chain and Biotin for Drug Delivery System

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高分子微胞在奈米尺度的藥物傳遞系統、生物顯影等應用扮演至關重要之角色。近年來利用設計高分子載體將藥物精準釋放於目標細胞及組織，用於治療癌症、動脈栓塞與減緩副作用等研究越來越受關注。本研究中首先透過帕瑟里尼(Passerini reaction)多組分合成設計具應答響應性之高分子微胞型藥物載體。使用二醛(A)，二羧酸(B)和異腈化物(C)，一步法或單批次獲得目標 ABC 序列的聚酯醯胺(Poly(ester amide) (PEA))；同時，透過不同單體選擇調節主鏈和末端官能基團，使其形成對序列具有高選擇、高整齊型的產物。在單體選擇上導入了雙硫鍵(Disulfide Bond)於主鏈上，使奈米高分子微胞具有氧化還原應答性。氧化還原應答的高分子已被確認能夠應用於藥物傳遞系統，可添加常用生化試劑二硫蘇糖醇(Dithiothreitol (DTT))後進行鑑定。第二部分，薑黃素(Curcumin)的優良抗氧化、抗發炎、對抗自由基侵害的作用，使其在癌症治療上發揮極大的功效，卻也因其疏水性導致應用的困難性，透過結合氧化還原應答奈米微胞載體的開發，成功達到細胞毒殺與優異的藥物包覆率，最後我們研究了奈米微胞的結構穩定性，透過動態光散射分析監測確認微胞具有超過 150 小時以上的穩定性。透過結合氧化還原應答及精準釋放奈米微胞載體的開發，解決因其疏水性導致應用的困難性並在癌症治療上發揮其優良抗氧化、抗發炎、對抗自由基侵害的作用。

**關鍵字:**多組分聚合、自組裝、奈米微胞、氧化還原應答、薑黃素

Polymeric nanoparticles play an important role in the nanoscale application such as drug delivery system (DDS), disease treatment, and bio-imaging. In recent years, the research of polymer container design which could release drugs into target cells is applying progressively in cancer treatment, atherothrombosis, and alleviation of side effect. This study focused on design of polymeric nanoparticles drugs containers with redox response via the one-step or one-pot multicomponent polymerization (MCP) based on Passerini reaction. By employing dicarboxylic acids (A components), dialdehydes (B components), and isocyanides (C components), a variety of ABC sequenced poly(ester amide)s (PEAs) can be facily obtained. In our designs, the main chain and end functional group can easily be adjusted via selecting different monomers. Some polymeric nanoparticles have redox-sensitive property due to the introduction of disulfide bonds. The degradation of nanoparticles will be determined in the presence of dithiothreitol (DTT). Curcumin (CUR), an effective and safe anticancer agent,



which was limited by its water insolubility, was loaded into the micelles as a model drug. The nanoscale polymeric micelles were confirmed by DLS. Faster intracellular CUR release was observed in the MCF-7 cells pretreated with GSH than in the untreated ones. In vitro WST-8 assays showed that the micelles were biocompatible and CUR-loaded micelles had higher cellular proliferation inhibition in HeLa cells. The developments of redox-response and targeting drug release nano-carriers expect to increase the efficacy of Curcumin treatment. We can expect the research project will be contributed to the cancer treatment application.

**Keywords** : Multicomponent polymerization (MCP), Self-assembly, Nano micelles, Redoxresponse, Curcumin

**探討丹參酚酸B鎂鹽在大鼠對於雙酚A誘導之代謝症候群之影響**

To explore the effects of magnesium lithospermate B on bisphenol A exposure-induced metabolic syndrome in rats

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肥胖與代謝疾病密切相關，而日常生活和產前暴露於內分泌干擾物質易導致肥胖。丹參酚酸 B 鎂鹽 (Magnesium Lithospermate B, MLB) 為丹參的活性萃取物，研究證實丹參酚酸 B 鎂鹽在餵食高脂飼料的大鼠動物模型中，能改善胰島素阻抗以及相關的代謝異常。由於在懷孕期間暴露於內分泌干擾物質雙酚 A 導致成年雄性後代葡萄糖和脂質代謝異常的情形與高脂肪飲食誘導的代謝異常類似，故本研究探討丹參酚酸 B 鎂鹽的補充是否能改善雙酚 A 在大鼠誘導的代謝異常。實驗使用懷孕的 Sprague-Dawley 大鼠，在懷孕期第 7 至 19 日每日腹腔注射 100 µg/kg/day 的 BPA 或是生理食鹽水，待其子代三週齡時離乳並在接下來四週的實驗期間分成四組：(1)產前暴露生理食鹽水並於飲水中給予生理食鹽水 (Control-Vehicle)；(2)產前暴露 BPA 並於飲水中給予生理食鹽水 (BPA-Vehicle)；(3)產前暴露生理食鹽水並於飲水中補充 30 mg/kg/day 之 MLB (Control-MLB)；(4)產前暴露 BPA 並於飲水中補充 30 mg/kg/day 之 MLB (BPA-MLB)。暴露於雙酚 A 的大鼠出現肥胖並同時伴有高血糖、高胰島素血症、胰島素抗性、高三酸甘油酯血症和血中游離脂肪酸升高等現象。除此之外，肝臟脂肪酸合成增加、脂肪酸氧化減少、活化脂肪細胞的脂肪生合成和成熟、以及減少肌肉對葡萄糖的攝取。而 MLB 補充改善了上述變化。此外，MLB 對糖皮質激素受體作用和發炎反應產生抑制作用，並促進脂肪組織中的脂肪分解和產熱。總結我們的研究結果證明 MLB 可能是一種潛在治療代謝疾病的化合物，包括母體暴露引起的代謝異常。

**關鍵詞：**丹參酚酸 B 鎂鹽；雙酚 A；代謝異常；營養品；內分泌干擾物質

Obesity is closely linked with metabolic diseases, while life and prenatal exposure to endocrine-disrupting chemicals has been implicated in the development of obesity. Magnesium Lithospermate B (MLB), an active compound of *Salvia miltiorrhiza* (Danshen), has beneficial effects on insulin resistance and metabolic abnormalities in diet-induced obese rodents. Since exposure to endocrine-disrupting chemical bisphenol A during pregnancy mimics the effects of high fat diet-induced alterations of glucose and lipid metabolism in adult male offspring, the effects of daily MLB supplementation for 4 weeks on metabolic abnormalities in rats weaning from prenatal bisphenol A-exposed dams were investigated. Bisphenol A-exposed rats developed obesity and adiposity concurrent with hyperglycemia, hyperinsulinemia, insulin resistance, hypertriglyceridemia, and elevation of circulating free

fatty acids. Increased hepatic fatty acid synthesis and decreased fatty acid -oxidation, activation of adipocytic adipogenesis, maturation, and lipogenesis, as well as reduction of muscular glucose uptake were demonstrated in bisphenol A-exposed rats. The aforementioned alterations were improved by MLB supplementation. Additionally, MLB displayed negative effects on glucocorticoid receptor action and inflammation, and promoted lipolysis and thermogenesis in the adipose tissues. In conclusion, our findings suggest that MLB may be a potential therapeutic compound against metabolic diseases, including maternal exposure-induced metabolic abnormalities.

**Keywords:** Magnesium Lithospermate B; Bisphenol A; metabolic abnormalities; nutraceutical; endocrine-disrupting chemical

## 探討Gefitinib對於CDK5過度表現之攝護腺癌穩定細胞株生長抑制敏感度的影響

The role of Gefitinib on prostate cancer cell growth through CDK5 regulation

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Cyclin-dependent kinase 5 (CDK5) 已被發現能調控前列腺癌細胞的生長與遷移，且能刺激 signal transducer and activator of transcription 3 (STAT3) 蛋白而加強前列腺癌的生長。先前研究指出，在前列腺癌細胞中 CDK5 的活性會影響其與 STAT3 的交互作用能力。Gefitinib (Iressa) 為控制細胞生長、細胞凋亡及血管新生的蛋白表皮生長因子受體 (Epithelial growth factor, EGFR) 的專一性抑制劑，在臨床上主要用以治療化療抗性的非小細胞肺癌之患者。近期研究指出 Gefitinib 的處理能降低癌細胞的增生能力及細胞數量、引發細胞週期 G1 期的停滯以及抑制其增生。而此研究目的在於探討 Gefitinib 對於 CDK5 蛋白的影響，以及其利用 CDK5 蛋白過表達之前列腺癌細胞株 22Rv1 探討其對於 CDK5 依賴性細胞的生長影響。本研究利用 Gefitinib 對於前列腺細胞株 22Rv1-EGFP-Vector 及 22Rv1-EGFP-CDK5 處理 24 小時，實驗結果發現穩定表達 CDK5 之前列腺癌細胞中，生長、增生與細胞週期相關蛋白有上升的趨勢。而 Gefitinib 的處理在 22Rv1-EGFP-Vector 的組別則發現有降低 p-S727-STAT3 蛋白表達的能力。此外，於穩定表達 CDK5 的細胞中則有對於 Gefitinib 抑制細胞增生的耐受性。我們也發現 Gefitinib 的處理能藉由抑制 CDK4 與 CyclinD1 蛋白導致細胞週期 G1 的停滯。研究發現 Gefitinib 能抑制一般癌症細胞株的生長功能，但不能抑制過度表達 CDK5 之 22Rv1 細胞株。總結來說，此研究指出 Gefitinib 於前列腺癌細胞導致的細胞增生、生長抑制作用與細胞凋亡的效果，在 CDK5 過度活化的條件下能有效被抵抗。

**關鍵詞：**Gefitinib, cell cycle arrest, CDK5, prostate cancer, cell proliferation

Cyclin-dependent kinase 5 (Cdk5) is known to regulate cell proliferation and metastasis in prostate cancer. It has been reported that CDK5 targets STAT3 which further promotes prostate cancer cell growth. Previous studies have showed that Cdk5 biochemically interacts with STAT3 and this interaction depends on Cdk5 activation in prostate cancer cells. Gefitinib (Iressa) is a selective inhibitor of epidermal growth factor, a growth factor that plays a pivotal role in the control of cell growth, apoptosis, and angiogenesis. Gefitinib is clinically used for the treatment of chemoresistant non-small cell lung cancer patients. Recently, treatment with Gefitinib was found to reduce proliferation and cell number of cancer cells, induced cell-cycle arrest in the G1 phase, and decreased cancer cell proliferation. Therefore, in this study, we investigated the role of Gefitinib on CDK5 regulation and CDK5-dependent prostate cancer

cell growth by using a CDK5-overexpressed 22Rv1-stable prostate cancer cell line. We treated the prostate cancer cell line 22Rv1-EGFP-Vector and 22Rv1-EGFP-CDK5 with Gefitinib for 24 h. Protein expression was observed in the case of 22Rv1 stably overexpressing CDK5 in terms of growth and proliferation-related proteins and, cell cycle-associated proteins. Gefitinib was found to reduce p-S727-STAT3 in cells of the vector group. On the other hand, stable overexpression of CDK5 tolerated the effect of Gefitinib on cell proliferation. We also found that Gefitinib treatment cause G1 cell-cycle arrest by reducing CDK4 and Cyclin D1 expression. It was found that Gefitinib could suppress tumor growth in normal cancer cells, but could not affect tumor growth in 22Rv1 cells in which CDK5 was overactive. In conclusion, this study demonstrates that Gefitinib inhibits cell proliferation and cell growth in prostate cancer cells and induces apoptosis, but CDK5 overactivation could protect the cells by partially resisting of Gefitinib.

**Keywords:** Gefitinib, cell cycle arrest, CDK5, prostate cancer, cell proliferation

**探討氯硝柳胺對調控信號傳導及轉錄活化蛋白3路徑在急性淋巴細胞白血病的機制**

The study of STAT3 pathway regulated by niclosamide in acute lymphoblastic leukemia

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T 細胞急性淋巴細胞白血病 (T-ALL) 是一種常見的兒科惡性腫瘤，其特徵是未成熟 T 細胞母細胞的異常存在。T 細胞急性淋巴細胞白血病的常規治療無法預防或治癒該疾病，第一次緩解後復發的風險很高。因此，需要醫療選擇來為患有 T 細胞急性淋巴細胞白血病的患者開發新的療法。氯硝柳胺(niclosamide)是一種傳統的口服抗蠕蟲藥物，據報導是一種潛在的抗癌劑，可調節細胞內信號通路。很少有研究調查氯硝柳胺對 T 細胞急性淋巴細胞白血病發展的影響。在這裡，本研究旨在調查氯硝柳胺對 T 細胞急性淋巴細胞白血病的抗白血病作用。我們首先假設氯硝柳胺對 T 細胞急性淋巴細胞白血病腫瘤生長的抑制作用是透過調節細胞自噬和細胞凋亡。在氯硝柳胺治療後，使用 MTT 測定法評估 T 細胞急性淋巴細胞白血病的細胞存活率，並使用膜聯蛋白 V/碘化丙啶染色評估細胞凋亡。在用氯硝柳胺處理的 T 細胞急性淋巴細胞白血病細胞中，通過蛋白質印跡分析細胞凋亡和細胞自噬相關蛋白的變化。此外，在體內模型中，T 細胞急性淋巴細胞白血病異種移植小鼠用於研究氯硝柳胺的抗白血病作用。結果表明，氯硝柳胺以劑量和時間依賴性方式顯著降低 Jurkat 和 CCRF-CEM 這兩種 T 細胞急性淋巴細胞白血病細胞之存活率。氯硝柳胺顯著活化 Jurkat (2  $\mu$ M) 和 CCRF-CEM 細胞 (1  $\mu$ M) 早期和晚期的細胞凋亡。更進一步，氯硝柳胺能以時間和劑量依賴性方式增加活化裂解的 caspase-3 和 LC3B，並且降低 Bcl-2 和 p62 的蛋白質表現，此外，氯硝柳胺在 Jurkat 和 CCRF-CEM 細胞中以劑量依賴性方式抑制 STAT3 蛋白表達。體內結果表明，氯硝柳胺治療透過活化裂解的 caspase-3 和 LC3B 顯著抑制 T 細胞急性淋巴細胞白血病異種移植小鼠的腫瘤生長和疾病進展。我們得出結論，氯硝柳胺具有抗白血病作用，它代表了一種治療 T 細胞急性淋巴細胞白血病的新方法。

**關鍵詞：**急性淋巴細胞白血病，氯硝柳胺，細胞凋亡，細胞自噬，信號轉導及轉錄活化蛋白 3

T-cell acute lymphoblastic leukemia (T-ALL) is a common pediatric malignancy, characterized by the abnormal presence of immature T-cell progenitors. Conventional treatments for T-ALL fail to prevent or cure the disease, with a high-risk of recurrence after the first remission. Thus, medical options are in demand to develop novel therapies for patients suffering with T-ALL. Niclosamide, a traditional oral anti-helminthic drug, has been reported to be a potential anticancer agent that regulates intracellular signaling pathways. Few studies

have yet investigated the effects of niclosamide on the development of T-ALL. Here, the present study aimed to investigate the anti-leukemia effects of niclosamide on T-ALL. We first hypothesized that the suppressive effects of niclosamide on the tumor growth of T-ALL are exerted by regulating autophagy and apoptosis. Following niclosamide treatment, T-ALL cell viability was evaluated using MTT assay, and apoptosis with Annexin V/propidium iodide staining. In T-ALL cells treated with niclosamide, changes in apoptosis- and autophagy-related proteins were analyzed by western blotting. In addition, in an *in vivo* model, T-ALL xenograft mice were used to study the anti-leukemia effects of niclosamide. The results showed that niclosamide significantly reduced the viability of Jurkat and CCRF-CEM T-ALL cells in both a dose- and time-dependent manner. Niclosamide significantly activated the early and late phases of apoptosis in Jurkat (at 2  $\mu\text{M}$ ) and CCRF-CEM cells (at 1  $\mu\text{M}$ ). Furthermore, niclosamide upregulated protein expression of cleaved caspase-3 and LC3B, while downregulated those of Bcl-2 and p62, in a dose-dependent manner in both Jurkat and CCRF-CEM cells. In addition, niclosamide inhibited STAT3 protein expression in a dose dependent manner in both Jurkat and CCRF-CEM cells. The *in vivo* results showed that niclosamide treatment significantly suppressed tumor growth and the disease progression in T-ALL xenograft mice by activating cleaved caspase-3 and LC3B. We conclude that niclosamide plays an anti-leukemia role, and that it represents a novel approach for the treatment of T-ALL.

**Keywords:** acute lymphoblastic leukemia, niclosamide, apoptosis, autophagy, STAT3

**探討三環類抗憂鬱劑杜使平對於小鼠血糖、血脂、胰島素、肝功能及非酒精性脂肪肝恆定之影響**

Study on the effects of a tricyclic antidepressant drug, doxepin on blood glucose, blood lipid, insulin, hepatic functional, and nonalcohol fatty liver disease homeostasis in mice

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杜使平 (doxepin) 為治療重度憂鬱症的三環類抗憂鬱劑，臨床上發現病患使用抗憂鬱劑治療會造成代謝上的失衡而導致肥胖及血糖增加等代謝症候群副作用。迄今為止，仍沒有足夠的資料探討杜使平對於肥胖及高血糖患者等影響，特別是對於惡化糖尿病和造成非酒精性脂肪肝等，其相關的分子生物學及病理學等機制。本研究利用 C57BL/6J 雄性小鼠，先建立肥胖小鼠模式，接續將肥胖小鼠分為對照組、杜使平組 (5 mg/kg/day) 兩組，了解服用杜使平時其對血糖及胰島素敏感性等代謝性影響之研究。透過每日管餵杜使平藥劑給予高脂飼料飼養的肥胖小鼠 8 週後，小鼠全部犧牲，採集血液後進行血清生化學、分子生物學及組織病理學等方式，評估杜使平對於代謝疾病的分子病理機制和胰島素訊息傳遞影響。研究結果顯示經每日管餵杜使平 (5 mg/kg/day) 肥胖小鼠相較對照組，有明顯增加體重、攝食量、肝臟重量、副睪脂肪重量、腹腔脂肪重量、脂肪肝程度、禁食血糖、胰島素阻抗指數、血清胰島素含量、血清血清素含量、血清三酸甘油酯含量、肝臟三酸甘油酯含量、脂肪酸合成酶表現量及肝臟脂質明顯增加等情況；另一方面管餵杜使平肥胖小鼠的胰島素敏感性指數、胰島素訊息傳遞蛋白 phospho-Akt、Akt、glucose transporter 4 及脂締素表現量等，則皆明顯低於對照組，上述這些結果證實杜使平會惡化肥胖、葡萄糖耐受性不良、胰島素阻抗等情形。因此，本研究以肥胖動物模式去模擬肥胖精神病患者使用杜使平治療時之副作用，以期未來能應用於評估臨床上使用杜使平作為精神病患藥物治療的考量，並提供作為杜使平導致血糖和脂肪肝病異常之後續研究基礎，同時進一步能提供做為及時預防措施，以減少國人因杜使平造成的代謝性疾病相關醫療資源的支出。

**關鍵詞:** 血糖、杜使平、胰島素、脂質、肝功能指數、非酒精性脂肪肝病

Doxepin is a tricyclic antidepressant for treating major depressive disorder—may have positive effects on blood glucose levels and obesity. To date, the full extent of the role of doxepin in leading to metabolic syndrome and nonalcoholic fatty liver disease has not been fully explored. Moreover, we do still unknown the mechanism of molecular biology and pathology in these metabolic side effects. In this study, we treated male high-fat diet (HFD)-fed C57BL/6J mice with doxepin (5 mg/kg/day doxepin) for 8 weeks to understand the effect of doxepin on metabolic parameters, insulin profiles, glucose metabolisms and obesity



changes using a high fat diet-fed C57BL6/J mice. We noted these mice to exhibit higher body weight, daily food efficiency, liver and epididymal fat pad weight, fasting glucose levels, HOMA-IR, serum insulin levels, serum serotonin levels, serum triglyceride levels, hepatic triglyceride levels, hepatic fat accumulation and fatty acid synthase expression when compared with HFD-fed control mice. Furthermore, doxepin-treated obese mice revealed a marked decrease in insulin sensitivity index, the activation of phospho-Akt, Akt, glucose transporter 4 and adiponectin expression. Notably, the treated mice showed higher glucose tolerance and blood glucose levels but lower glucose transporter 4 expression. In conclusion, doxepin may result in exacerbation of diabetes syndrome with glucose intolerance. Furthermore, these finding will help to establish the foundations association with the researches of doxepin induced blood glucose abnormal and nonalcoholic fatty liver disease in patients. Furthermore, the obtained information will be valuable in providing new insights into prevent doxepin induced metabolic disease in patients and a better reduces in medical treatment cost.

**Keywords :** blood glucose, doxepin, insulin, lipid, liver function index, non-alcoholic liver disease

**植基於深度學習之乳癌超音波影像偵測與診斷**

Breast Tumor Detection and Diagnosis Based on ultrasound Image and Convolutional Neural Networks Deep Learning Model

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乳癌是全世界確診率第二高的癌症，而乳房超音波檢查是診斷乳癌最常使用的方式之一。以往在診斷乳癌時需要由經驗豐富的放射科醫師來進行超音波影像的判讀，但人工判讀費時費力，也有可能因為雜訊或假影等而造成誤判，因此一個輔助診斷工具至關重要。本研究收集了 80 位女性患者共 2300 張乳房超音波影像，包括 1800 張腫瘤影像及 500 張正常影像，並且比較了兩種卷積神經網路模型，包括 Faster R-CNN、RetinaNet 在乳房超音波影像上偵測腫瘤之效能。在實驗中利用自動資料增量技術擴增資料以提升模型的強健性；使用遷移學習、SGDR 提升模型的穩定度並且增加訓練效率。研究分析了多種卷積神經網路應用於偵測乳房超音波影像腫瘤之模型，並從中挑選出效能最佳者，可作為乳癌診斷之輔助工具，希望可以協助醫師減少判讀超音波影像的時間並且更準確地診斷乳房腫瘤，從而協助患者及早接受治療。

**關鍵詞：**乳房超音波影像、卷積神經網路、腫瘤偵測、RetinaNet、Faster R-CNN、CIoU 損失函數

Breast cancer is the second leading diagnosed cancer around the world, and breast ultrasound is one of the most commonly used technique for its diagnosis. In the past, radiologists merely interpret ultrasound images manually, which is time consuming, laborious, and may cause misjudgments due to noise or artifacts. Therefore, auxiliary diagnostic tools are necessary for radiologists to increase the preciseness of manual interpretations. This study collected 2300 breast ultrasound images (1800 tumors and 500 normals) from 80 female patients. Two convolutional neural network models: Faster R-CNN and RetinaNet are utilized for tumor detection of breast ultrasound images. The Autoaugment improves the robustness of the model, and transfer learning and SGDR enhance model stability and training efficiency. This study proposed various convolutional neural network models for breast tumors detection of ultrasound images and suggested the best -performing model for the auxiliary tool of the breast cancer diagnosis. By adopting those models to interpret ultrasound images, doctors could reduce time in diagnosis and provides early treatment for the patients.

**Keywords:** Breast Ultrasound Image, Convolutional Neural Network, RetinaNet, EfficientDet, Tumor Detection, CIoU Loss Function

## 以雲端運算為基礎之深度學習醫療資訊建模平台之研究

Cloud-Computing-based Healthcare Information Modeling Platform of Deep Learning

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隨著生醫資訊(Bioinformatics)的蓬勃發展，醫療產業也進行了各種不同應用的拓展與進化，其業務涵蓋了掛號、問診、病例(如雲端藥歷、檢查檢驗紀錄等)、手術(如 機器人手術系統)、門診流程、醫療設備(如智慧病房)、照護(如互聯設備)…等，而分析人們的醫療數據進而達到智慧醫療已成為現今產、官、學界的一門重要課題。然而，由於醫療相關資料具有巨量資料的特性(4Vs)，分別為：資料量大(High Volume)、資料量成長速度快(High Velocity)、資料類型多(High Variety)、資料真實性不確定(Uncertain Veracity)。根據上述的特性，我們可以了解到所謂巨量資料，一言以蔽之就是技術上不可能透過簡單的技術，且在單一機器上完成分析的資料就能稱為一種巨量資料。然而，在雲端架構下建構醫療資訊分析模型與建構投資行為模型並不一樣，但不論建構何種資料的模型，通常，構建醫療相關資料分析模型不僅需要深度學習，而且還需要轉移學習技術。因此，本計畫預計提出一系列具有轉移學習方式的深度學習技術，用於大數據分析，以使我們基於雲計算的平台在構建醫療相關資料分析模型上具有可應用性。所提出的深度學習技術可用於分析跨疾病的病歷。我們可以將醫療記錄的分析結果應用於許多實際應用中，例如 AI 診所。因此，我們可以預期這樣基於醫療相關資料分析平台與其深度學習應用的擴充，不僅能造福醫療產業，更能使其服務品質大幅提升。

**關鍵詞：**深度學習，轉移學習，生醫資訊，巨量資料分析，醫療資訊建模，雲端運算

With the advance in bioinformatics, the health care industry has expanded and evolved a variety of different modern medical services. Analyzing people's medical records has become the emerging research fields that attract a lot of attentions. However, it is not easy to analyze people's medical records through modern bioinformatics technology. The reason is that the data collected from medical services always has big data properties, i.e., High Volume, High Velocity, High Variety, Uncertain Veracity. According to above-mentioned 4Vs issues, the analysis of big data can not rely on a single computer. Accordingly, we have built a cloud-based platform for analytics of big data. However, constructing medical data analysis model is quite different from constructing investment behavior model. Usually, constructing medical data analysis model requires not only deep learning but also transfer learning technology. Therefore, in this project, I plan to propose a series of deep learning technologies with transfer learning manner for analysis of big data to make our cloud-computing-based platform substantial. The proposed deep learning technologies can be utilized for analyzing

medical records with various multiple diseases. We can apply the analysis result of medical records for many real-world applications such as AI clinic. Therefore, we expect that our proposed algorithm and application for improving cloud-computing-based platform not only benefit the medical industries but also improve the quality of their services.

**Keywords :** Deep Learning, Transfer Learning, Bioinformatics, Big Data Analysis, Medical Data Modeling, Cloud Computing

**探討溶癌病毒家禽里奧病毒於不同癌細胞株之複製及癌細胞株之病毒受體**

Study on the replication of oncolytic avian virus in different cancer cell lines and the virus receptor of cancer cells

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家禽里奧病毒 (Avian reovirus; ARV) 及 mammalian reovirus(MRV) 已被證實為溶癌病毒 (oncolytic virus)。ARV 為非人畜共通感染之病毒，因此人類不會有 ARV 之背景抗體，值得深入研究及建立 ARV 應用於抗癌研究及臨床應用。本研究團隊前期研究已初步證實 ARV 可影響 HeLa 及 A549 癌細胞株之 cell cycle 及減少 A549 癌細胞於 nude mice 之生長，而抑制腫瘤大小。上述病毒都有明確的 receptors 協助進入細胞內部，但 ARV 之 cell receptors 尚未知。本計畫除進一步探討確認 ARV 可感染那些人類癌細胞及其感染效價外，也擬研究鑑定 ARV 感染不同癌細胞之細胞受體。本研究共使用株 7 人類癌細胞株(HeLa、A549、AGS、HepG2、HAP1、PC3 及 MCF7)、1 株小鼠黑色素瘤細胞(B16-F10)及人正常肺纖維芽母細胞(human lung fibroblast)。研究結果證實 ARV 可感染多種癌細胞株 (HeLa、A549、AGS、HepG2、HAP1 及 B16-F10) 但不會感染人之肺纖維芽母細胞，被感染癌細胞株其病毒力價可達 105.12-6.4 PFU/mL。本研究也證實 ARV 不會感染 PC3 及 MCF7 癌細胞株。藉由 LC/MS/MS 及病毒疊加蛋白結合分析 (Virus overlay protein binding assay, VOPBA) 來分析可能之 cell receptor。以 VOPBA 來預測病毒結合的蛋白，發現在 65 及 32 kDa 左右有一條與 ARV 蛋白 sigma C 結合的訊號。將此兩條帶之蛋白回收及藉由 LC/MS/MS 定序得知為 ANXA 蛋白家族 (ANXA1、ANXA2、ANXA5) 及 ADGRL2 蛋白。為進一步確認 ANXA 蛋白家族 (ANXA1、ANXA2、ANXA5) 及 ADGRL2 蛋白是 ARV 之細胞受體，以 shRNAs 阻斷 ANXA 家族及 ADGRL2 蛋白表現或以單株抗體來遮蔽上述細胞膜上之受體，結果證實可抑制病毒進入癌細胞，且病毒力價降低 2-3 log。證實 ANXA 家族及 ADGRL2 蛋白是 ARV 之 cell receptors，可調控 ARV 感染人類癌細胞。

Avian reovirus (ARV) and mammalian reovirus (MRV) have been identified as oncolytic viruses. ARV is a non-zoonotic virus, so humans do not have ARV background antibodies. Therefore, it is worthy of in-depth research and establishment of ARV for anti-cancer research and clinical applications. Preliminary studies by our research team have demonstrated that ARV retards the cell cycle of HeLa and A549 cancer cell lines and inhibits the growth of A549 cancer cells in nude mice, which reduces tumor size. MRVs have clear receptors to assist in entering the cell, but ARV has not yet identified its cell receptors. In addition to further research to confirm which human cancer cells can be infected by ARV and its infection titer,

this project also intends to study and identify the cellular receptors for ARV to enter and infect different cancer cells. Seven human cancer cell lines (HeLa, A549, AGS, HepG2, HAP1, PC3 and MCF7), one mouse melanoma cell line (B16-F10), and human lung fibroblasts were used in this study. Our results reveal that ARV can infect a variety of cancer cell lines (HeLa, A549, AGS, HepG2, HAP1, and B16-F10) but not human normal lung fibroblasts or PC3 and MCF7 cancer cell lines. Our data show that the virus titers of infected cancer cell lines can reach  $10^{5.12-6.4}$  PFU/mL. The possible cell receptors were analyzed by LC/MS/MS and virus overlay protein binding assay (VOPBA). Using VOPBA to predict the virus-binding protein, it was found that there is a signal binding to the ARV protein sigma C at around 65 and 32 kDa. These proteins at these two band positions were recovered and sequenced by LC/MS/MS and identified as ANXA protein family (ANXA1, ANXA2, and ANXA5) and ADGRL2 proteins. To further confirm these proteins on the cell membrane are involved in cell entry of ARV, the expression of ANXA family and ADGRL2 proteins was blocked by shRNAs or monoclonal antibodies were used to shield the receptors ANXA family and ADGRL2 proteins on the cell membrane. Our results reveal that cell entry of ARV into cancer cells was suppressed, and the virus titer is reduced by 2-3 logs. This study suggests ANXA family and ADGRL2 proteins are cell receptors that are involved in the entry of ARVs into cancer cells.

**評估新穎 EGFR交互作用蛋白TNFAIP2用於提升鼻咽癌細胞對於EGFR標靶治療效果的潛力**

Evaluation of the potential of a novel EGFR-interacting protein TNFAIP2 in enhancing EGFR-targeted therapeutic response of nasopharyngeal carcinoma cells

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TNFAIP2 (腫瘤壞死因子誘發蛋白質第二型)被認為能參與發炎反應及血管新生，首度被發現在鼻咽癌組織中過量表現，與病患預後不佳高度相關。我們鑑定出表皮生長因子受體(EGFR)為嶄新的 TNFAIP2 交互作用蛋白。EGFR 在九成之鼻咽癌組織表現，其表現量與預後呈負相關。由於鼻咽癌患者被診斷時多為中後期，約三成患者對標準治療反應不佳，EGFR 已被評估作為標靶治療標的，但最終會產生抗性。我們的研究結果顯示，在 TNFAIP2 基因減弱或基因剔除的鼻咽癌細胞株中，EGFR 在細胞膜上的比例降低，影響 EGF 引發 EGFR 之自體磷酸化、內化與胞內運輸，以及下游 ERK1/2 被吸引至細胞膜與磷酸化程度；而 EGF 引發之細胞移動亦明顯降低。我們進一步證明 TNFAIP2 主要透過 C 端 521 至 654 胺基酸序列，與 EGFR2 的激酶結構域(kinase domain)和近膜結構域(juxtamembrane domain)進行交互作用；同時表現 TNFAIP2 與 EGFR 之激酶結構域會抑制細胞移動能力，顯示 TNFAIP2 可能透過兩者間之交互作用調控 EGFR 的功能。本計畫已建立了評估 TNFAIP2 對於 EGFR 標靶藥物影響的鼻咽癌細胞系統，將繼續以腫瘤小鼠模型探討 TNFAIP2 在鼻咽癌治療上的潛力。

**關鍵詞：**腫瘤壞死因子誘發蛋白質第二型(TNFAIP2)，鼻咽癌，表皮生長因子受體(EGFR)，蛋白質交互作用，細胞移動

TNFAIP2 (TNF- $\alpha$ -inducible protein 2) is identified as a pro-angiogenic and pro-inflammatory factor. Cancer-associated overexpression of TNFAIP2 is first demonstrated in nasopharyngeal carcinoma (NPC) and is significantly correlated with a poor survival. We identified EGFR (epidermal growth factor receptor) as a novel interacting partner of TNFAIP2. EGFR is expressed in over 90% cases of NPC, and overexpression of EGFR is associated with a poorer prognosis. Given that most of NPC patients are diagnosed of NPC at locoregionally advanced status (stage II-III), and approximately 30% of them show poor response to the standard recommended treatment, EGFR has been evaluated as a therapeutic target in NPC. However, these treatments usually lead to drug resistance. This study reveals the cell-surface proportion of EGFR was reduced in TNFAIP2-knockdown (KD) or TNFAIP2-knockout (KO) NPC cell lines, which impaired the EGF-induced autophosphorylation and internalization of EGFR, and membrane recruitment and phosphorylation of downstream ERK1/2. Moreover, the EGF-induced cell motility was also reduced in TNFAIP2-KD or TNFAIP2-KO cells. We

further demonstrated that the interaction between TNFAIP2 and EGFR requires the C-terminal amino acids 521 to 654 of TNFAIP2 and the kinase domain and the juxtamembrane domain of EGFR. Co-expression of TNFAIP2 with the EGFR kinase domain inhibited cell motility, highlighting the possibility that TNFAIP2 modulates the function of EGFR via a protein-protein interaction. Collectively, this project has established NPC cell models to evaluate the impact of TNFAIP2 on EGFR-targeted therapies, and will further verify whether TNFAIP2 can potentiate the therapeutic response of NPC cells using relevant NPC xenograft mouse models.

**Keywords:** TNFAIP2, nasopharyngeal carcinoma, EGFR, protein interaction, cell motility



## 母乳菌相及腸道菌相對早產兒消化能力之影響

Efeefcts of microflora in human milk and intestine on the digestibility of preterm infants

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本研究比較早產兒及足月兒腸道(糞便)菌相之差異，並假設消化能力較佳之早產兒其腸道菌相較類似於足月兒。台中榮民總醫院小兒科篩選13位懷孕週數小於37周，出生體重小於等於2500公克之早產兒，另外10位足月兒作為對照組，於一周齡至四周齡時每周各收集一次糞便，交與靜宜大學食品營養學系進行DNA抽取及DNA品質確定後送至生技公司進行16S rDNA定序(metagenomic sequencing, MGS)並透過資料庫分析菌相分析。台中榮總則於新兒出生之二月齡內，每日記錄進食量並以全靜脈營養 (total parenteral nutrition)使用情況及餵食達到full feeding (100-120ml/kg/day)之時機評估其消化能力。早產兒糞便菌相之分布與早產兒進食量 (消化能力)等數據進行相關性分析。結果顯示，早產兒和足月兒之糞便菌相顯著不同，與早產兒相比，足月嬰兒具有更高的微生物群多樣性。早產兒糞便之優勢菌種為Proteobacteria門、Bacilales科中之 Paenibacillaceae、Clostridia屬 及Actinobacteria門；足月兒糞便之優勢菌種則以消化菌為主，包括Firmicutes門、Bacteroides屬及Actinobacteria門。早產兒消化率差組和消化率佳組之糞便菌相亦具顯著差異，消化率佳之早產兒糞便中含較高之消化相關細菌，並以Firmicutes門為主，而消化率差的早產兒糞便中則富含志賀氏菌和鞘氨醇單胞菌等伺機性致病菌。

**關鍵詞：**早產兒、足月兒、糞便菌相、消化能力、次世代定序

This study compared the differences in the gut (fecal) microbiota of preterm and full-term infants, and assumed that preterm infants with better digestion had a similar gut microbiota to term infants. The Pediatrics Department of Taichung Veterans General Hospital(TVGH) screened 13 preterm infants with a gestational age of less than 37 weeks and a birth weight of less than or equal to 2500 g, and another 10 full-term infants as a control group. They were handed over to the Department of Food and Nutrition at Providence University for DNA extraction and DNA quality determination, and then sent to a biotechnology company for 16S rDNA sequencing (MGS) and bacterial phase analysis through database analysis. TVGH recorded the daily intake of infants within two months of birth and evaluated their digestive ability by using total parenteral nutrition and when the feeding reaches full feeding (100-120ml/kg/day). The distribution of fecal microbiota in premature infants was correlated with data such as food intake (digestive ability) of premature infants. The results showed that

the fecal microbiota profiles of preterm and term infants were significantly different from full-term infants. Full term-infants showed higher microbiota diversity compared to preterm infants. The dominant bacterial species in the feces of premature infants were Proteobacteria, Paenibacillaceae, Clostridia and Actinobacteria. There were also significant differences in the fecal microbiota between the preterm infants with poor digestibility and the ones with good digestibility. Feces from high digestibility preterm infants contained higher levels of digestion-related bacteria, mainly in Firmicutes, whereas feces from preterm infants with poor digestibility were conversely rich in opportunistic pathogens, such as *Shigella* and *Sphingomonas*.

**Keywords :** Preterm infants, full-term infants, fecal microbiota, digestibility, next-generation sequencing

**具深度學習之糖尿病患視網膜病變影像辨識技術研究**

A Study on Recognizing Diabetic Retinopathy Images using Deep Learning

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糖尿病所引發的視網膜病變也是目前非常嚴重的問題，若能透過深度學習在視網膜斷層掃描影像上辨識糖尿病所引起的病變，就可以及早治療，則可以避免惡化至失明。本計畫的主要目標就是針對這國內嚴重的眼睛疾病，透過眼底視網膜影像，使用深度學習技術來辨識它們。本計畫是一個一年期研究計畫，將與台中榮總團隊眼科部林耿弘主任醫師團隊一同進行研究。主要目標是收集眼底Angio視網膜斷層掃描影像，並使用卷積神經網路針對眼底Angio視網膜斷層掃描影像進行訓練，用以辨識糖尿病視網膜病變的徵兆。目前已完成初步模型訓練，未來將訓練完成之辨識模型開發成軟體系統，並且在台中榮總進行測試與模型調整，並跟眼底視網膜斷層掃描儀器廠商合作，將相關技術導入儀器中。

**關鍵詞：**糖尿病視網膜病變，視網膜斷層掃描，深度學習，卷積神經網路

Diabetic retinopathy is a very serious issue in the world. If patients can be diagnosed as diabetic retinopathy in early stage from Angio optical coherence tomography images by using deep learning, they can be treated early before going blind. The goal of this project is to detect such retinal diseases through Angio optical coherence tomography images by using deep learning. This is a one-year project, and the department of Ophthalmology in Taichung Veterans General Hospital is the research partner in this project. The goal of this project is to collect Angio optical coherence tomography images, label them, train a model for classifying diabetic retinopathy by using convolutional neural network. A prototype trained model is established now and in the future we can develop a system with this well-trained model, and the system can be verified by the partner in the department of Ophthalmology in Taichung Veterans General Hospital. Then, this system is expected to be integrated into Angio optical coherence tomography machines.

**Keywords :** Diabetic Retinopathy, Optical Coherence Tomography, Deep Learning, Convolutional neural network

**紅藜對老化伴隨脂肪肝模式脂質代謝相關調控分子機制之影響**

Effects of Djulis on lipid metabolic signaling in aging with fatty liver model

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老化會引發許多正常代謝過程的變化，進而衍生更多的慢性疾病如非酒精性脂肪肝病(Non-alcoholic fatty liver disease, NAFLD)的發生。紅藜 (Djulis)含有豐富的活性成分，可以通過增強抗氧化和減少細胞凋亡來降低氧化壓力，同時具有抗疲勞、降低脂質、緩解代謝症候群、調節免疫及保護大鼠免受 CCl<sub>4</sub> 造成的肝損傷等作用。我們先前的研究結果顯示老化且伴隨脂肪肝動物模式-SAMP8 小鼠，在補充紅藜後會增加其肝臟中自噬因子並降低凋亡反應。此外，紅藜也改善了血清中的肝損傷指標及降低脂肪肝指數，但其對脂質調控機制的相關影響則尚不清楚。因此，本次計畫繼續以紅藜為材料，探討紅藜對 SAMP8 小鼠肝臟脂肪代謝相關調控因子之影響。實驗將 3 月齡 SAMP8 小鼠分為對照組及添加三個不同劑量的紅藜組，為期十二週。結果顯示，紅藜可藉由提升肝臟中過氧化物酶體增植物激活受體  $\alpha$  (Peroxisome proliferator-activated receptor  $\alpha$ , PPAR- $\alpha$ )，進而改善改善成纖維細胞生長因子(Fibroblast growth factor 21, FGF21)和  $\beta$  克洛素( $\beta$ -Klotho,  $\beta$ KL)的表現，且會下調氧化物酶體增植物激活受體  $\gamma$  (Peroxisome proliferator-activated receptor  $\gamma$ , PPAR- $\gamma$ )，進而抑制甾醇調節元件結合蛋白 1c (Sterol regulatory element-binding protein 1c, SREBP-1c)和脂肪酸合酶(Fatty acid synthase, FAS)的表現，並降低結合蛋白 CCAAT/enhancer binding protein (C/EBP)之含量。此外，亦有改善血清中瘦素(leptin)和脂聯素(adiponectin)的趨勢。綜合上述，補充紅藜可能透過改善肝臟中脂質代謝訊息因子的表現，進而達到預防老化導致的非酒精性脂肪肝之效益。

**關鍵字：**非酒精性脂肪肝疾病、紅藜、老化促進小鼠、脂質代謝訊息因子

Aging usually accompanying with gradually physiological degradation, which may lead the incidence of chronic diseases such as non-alcoholic fatty liver disease. Djulis contained abundant active components which could reduce oxidative stress by enhancing antioxidant and suppressing apoptosis, and had been proved with many beneficial effects, such as anti-fatigue, reducing lipid levels, lessening metabolic syndrome, regulating immune function, and protecting liver to avoid the CCl<sub>4</sub> induced damage. Our previous results indicated that Djulis increased autophagy and reduced apoptotic factors in the aging with fatty liver model-senescence accelerated prone mice (SAMP8), and also reduced serum liver injured indicators and fatty liver score. However, the related mechanism of Djulis on the lipid modulation is still unclear. This study aims to investigate the effect of Djulis on the related signaling of

lipid metabolism by SAMP8 mice. Three month old SAMP8 mice was divided into control and three different doses of Djulis groups, and fed for 12wks. The results shows that Djulis improves the expressions of fibroblast growth factor 21 (FGF21) and  $\beta$ -klotho ( $\beta$ KL) by increasing the peroxisome proliferator-activated receptor  $\alpha$  (PPAR- $\alpha$ ) level in the liver. Djulis downregulates the peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ ), inhibits the sterol regulatory element-binding protein 1c (SREBP-1c) and fatty acid synthase (FAS) expressions, and reduces CCAAT/enhancer binding protein (C/EBP) level. Moreover, Djulis also tend to improve the serum leptin and adiponectin levels. In conclusion, Djulis supplementation may improve the hepatic lipid metabolic signaling to preventing the prevalence of non-alcoholic fatty liver disease associated with aging progression.

**Keyword:** non-alcoholic fatty liver disease, Djulis, Senescence-accelerated mice prone 8, lipid metabolic signaling

## TCVGH-PUI108104

### 以人工智慧深度學習方法建構高品質心肺復甦術教學即時回饋系統

Real-time Feedback System on Training for High Quality Cardiopulmonary Resuscitation with Deep Learning Approaches

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根據美國近年來「生命之鏈」觀念，在心臟及呼吸停止之狀態，人的腦細胞於 4 分鐘開始死亡，於 10 分鐘內腦死成為定局。因此，心肺復甦術(Cardio Pulmonary Resuscitation, CPR)對於因疾病或意外事故導致心臟停止跳動的病患而言，通常是必要且迫切的一種急救措施。目前心肺復甦術是採用美國心臟學會公布的新版心肺復甦術操作準則。在此準則中提出之施救程序，特別強調先施行「胸部按壓」的步驟，以確保病患體內之血液循環，使含氧血流可供應各器官。因此，高品質 CPR 要求對於急救之品質至關重要。此外，CPR 能否成功的救治更多病患，其前提在於讓更多一般民眾確實學會 CPR 並能成功地運用此技巧，使其能在緊急狀況下可成為施救者，對病患施行 CPR，以爭取更多的救治時間。然而，如何有效地教導與訓練 CPR 學習者達到高品質 CPR 的目標，單靠 CPR 的合格師資仍顯不足，因此，開發具有影音導引功能的教學系統顯得格外重要。基於去年已成功導入深度學習技術於判定人因姿勢危害，今年進一步導入 CPR 胸部按壓姿勢之精準判定。在本研究中，我們提出以二維人體姿態估計深度學習方法，建構一個高品質 CPR 教學即時回饋系統，進行 CPR 動作姿勢的影像辨識訓練，讓機器自動學習判斷 CPR 學習者，是否符合高品質 CPR 的要求並給予即時性的教學回饋，使 CPR 學習者可以依照回饋的指示，即時修正錯誤的姿勢，逐步練習達到高品質 CPR 的目標。

**關鍵詞：**心肺復甦術，人體姿態辨識，深度學習，急診醫學，高品質 CPR

According to the concept of "The Chain of Survival", when the heart and breathing are stopped, human brain cells begin to die in 4 minutes, and brain death within 10 minutes is a foregone conclusion. Thus, Cardio Pulmonary Resuscitation (CPR) is usually a necessary and urgent first aid measure for patients whose heart stops beating due to diseases or accidents. At present, CPR adopts the new version of CPR operating guidelines published by the American Heart Association. The rescue procedure proposed in this guideline particularly emphasizes the first step of "chest compression" to ensure blood circulation in the patient's body so that oxygenated blood can supply various organs. Thus, high-quality CPR requirements are critical

to the quality of first aid. In addition, whether CPR can successfully treat more patients is based on the premise that more ordinary people can actually learn CPR and can successfully use this technique, so that they can become rescuers and implement CPR on patients in emergency situations, in order to gain more treatment time. However, how to effectively teach and train CPR learners to achieve the goal of high-quality CPR is still insufficient for CPR qualified teachers alone. Therefore, it is particularly important to develop a teaching system with audiovisual guidance functions. Based on the successful implementation of deep learning technology to determine human pose estimation last year. This year, we will further introduce the accurate determination of CPR chest compression posture. In this study, we propose a deep learning approach of 2D human pose estimation to construct a high-quality CPR teaching and real-time feedback system, and perform image recognition training of CPR actions, so that the machine can automatically learn to determine whether CPR learners meet high-quality CPR. It also provides immediate teaching feedback, so that CPR learners can immediately correct wrong poses according to the feedback instructions, and gradually practice to achieve the goal of high-quality CPR.

**Keywords:** Cardio Pulmonary Resuscitation, Human Pose Estimation, Deep Learning, Emergency Medicine, High-Quality CPR

## **人工智慧深度神經網路機器學習法用於判讀單導程心電圖心律不整疾病的預測和分類**

Artificial Intelligence Deep Neural Networks for Detection and Classification of Cardiac Arrhythmia Disorders in Single-lead Electrocardiography

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心血管疾病是全球最常見的死因之一，而心電圖（ECG）是其最主要的診斷工具。儘管標準的 12 導程心電圖可以全面評估心臟的電氣活動，但其在緊急情況下的可用性卻有限。在緊急情況下，例如在急救室、救護車、直升機和發生院外心臟驟停的偏遠地區，單導程心電圖相對容易獲得，可提供主要有關心律疾病和心臟再極化疾病的信息。然而，第一線的醫學技術人員仍然很難準確判讀單導程心電圖傳遞的信息，甚至導致延誤了有效的治療。而第一線和急診部門的專業人員在於判讀單導程心電圖方面的診斷能力也很有限，這是一個亟待解決的臨床問題。

人工智慧(AI)深度神經網路(DNN)的機器學習(ML)，可以幫助電腦學習和制定規則，而無需人工程序的介入指導。與傳統方法相比，人工神經元網路演算法可使用更多的神經元層次來適應大型、多樣化和複雜的數據集。此類技術可以改善醫療保健和臨床實務。而監督式學習模型可以基於已標註的案例輸入輸出對，學習將輸入資料映射到輸出端，對於在單導程心電圖上檢測和分類疾病是理論上可行的。

本研究的目的是，通過深度神經網路的機器學習，來分析單導程心電圖去識別 10 種常見的心律不整疾病，從而提高預測準確度，促進有效而準確的治療。在這項研究的第一階段，我們將分析 100 例確認為心律不整患者的單導程心電圖。在第二階段，我們將使用經過訓練後的機器學習模型，通過深度神經網路的機器學習來預測單導程心電圖心律不整診斷的敏感性/特異性。我們假設與傳統的人力的常規判讀相比，機器學習模型可能會提高心律不整疾病的檢測和分類的準確性。

本研究在 ECG 影像中自動判別與框出心律不整位置，預測結果各心律類別按 recall 的排序之整體 precision 平均 mAP 可以達到 50.74%，其中的 N 類別的 AP 值可以達到 87.17%。期望未來能更加提升此模型的預測效能以輔助醫療人員，減輕其負擔並減少誤判，減少生命的損失。

**關鍵字:**十二導程心電圖(12-lead ECG)；心律不整(Arrhythmias)；人工智慧(Artificial intelligence, AI)；深度神經網路(Deep neural network, DNN)；機器學習(Machine learning, ML)；YOLOv

Cardiovascular diseases are the leading cause of death worldwide<sup>1</sup> and the electrocardiogram (ECG) is a major tool in their diagnoses. Despite the standard 12-lead ECG could provide a full evaluation of the cardiac electrical activity, its availability in emergency situation is limited. In emergent situation such as in ambulance, helicopter, and rural area where out-of-hospital cardiac arrest happened, a single-lead ECG is easy to obtain to provide



mostly about cardiac rhythm and repolarization disorders. However, interpretation of a single-lead ECG by emergent medicine technicians remained difficult to be accurate, leading a delayed in efficient therapy. Primary care and emergency department health professionals also have limited diagnostic abilities in interpreting the single-lead ECG.

Artificial intelligence machine learning (ML) with deep neural networks (DNN) helps computers learn and develop rules, without having to be instructed every step of the way by human programmers. A class of artificial neural network algorithms uses more layers than traditional approaches to suite for large, diverse, and complex datasets. Such technology may improve health care and clinical practice. Supervised learning models, which learn to map an input to an output based on example input–output pairs, is feasible for detection and classification of diseases on single-lead ECG.

The aim of this study is to improve the prediction accuracy with DNN-based interpretation of a single-lead ECG to identify 12 types of arrhythmias, to facilitate an efficient and accurate treatment. In the first phase of this study, we will enroll 100 patients' single-lead ECGs with a correct label of arrhythmia by specialists for ML with DNN. In the second phase, we will use the trained ML model to estimate sensitivity/specificity in predicting arrhythmias on single-lead ECG. We hypothesize that ML model might improve the accuracy to detect and classification of arrhythmia compared to conventional interpretation by primary care technicians.

The trained model can identify and locate the positions of arrhythmia automatically. As a result, the overall mean of Average Precision (mAP) can reach 50.74%, and the AP value of the N category can reach 87.17%. In the future, we expect to promote the performance of our model and then it can assist medical staff to quickly confirm the cardiac arrhythmia, reduce their burden, and reduce misidentification and the loss of lives.

**Keywords:** 12-lead ECG; Arrhythmias; Artificial intelligence; Deep neural network; Machine learning; YOLOv

**評估芳烴受體配體來緩解神經性疼痛的可行性**

The assessment of aryl hydrocarbon receptor ligand omeprazole in alleviating the neuropathic pain

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**研究的目的：**

眾所周知，神經性疼痛是軀體感覺系統所涉及的損害，通常被定義為由原發性病變或神經系統功能障礙所引起的疼痛。當前，尚無完整且決定性的臨床療法。芳烴受體 (AhR) 是一種蛋白質，屬於 PAS (Per-ARNT-Sim) 家族，包含一個基本的螺旋-環-螺旋結構域。AhR 在神經系統中的調節機制，不僅取決於內部刺激，還取決於外部刺激，例如腦外傷 (TBI) 或中風則會增加 AhR 的表達。在我們先前的研究中，我們發現神經受到慢性壓傷，從皮膚到脊髓以及腦的體感皮層的炎症反應，發生了顯著變化。然而，尚未確定在慢性神經損傷模型中對 AhR 的調節的廣泛研究。

**研究的方法：**

在這項研究中，我們使用了野生或 AhR 基因剔除的小鼠，在神經體外培養和慢性神經損傷來研究 AhR 表達在神經系統中的作用，並使用 AhR 配體(奧美拉唑)評估其對神經性疼痛的治療效果。這項研究有三個目標。首先，我們研究 AhR 基因剔除的神經組織及加入 AhR 配體於神經組織中研究神經變性和氧化應壓力的作用。其次，我們評估了具有 AhR 基因剔除及接受奧美拉唑治療的動物的神經行為和電生理的表現。第三，我們測量了 AhR 基因的組織形態學改變或相關蛋白表達的作用。

**研究的結果：**

在神經體外的培養中，AhR 基因剔除增加了神經退縮的數目，奧美拉唑則減緩野生型和 AhR (+/-) 的退化性病變，但對 AhR (-/-) 則沒有影響。在機械性異常性疼痛和熱痛覺過敏的測試中，AhR (+/-) 或 AhR (-/-) 易引起疼痛的超敏感性。AhR 基因剔除增加了體感誘發電位的強度。肌肉重量的測量則顯示，AhR (+/-) 或 AhR (-/-) 的小鼠的體重顯著下降。在受傷的神經中，觀察到了野生型的神經中的 AhR 的蛋白有顯著的表達，但是在 AhR (-/-) 的神經，則無明顯的反應，而 AhR (+/-) 只有微量的增加。在組織形態學分析中，AhR (+/-) 和 AhR (-/-) 顯著的增加 CD 68, NGFR 和 TNF- $\alpha$  的表達。相反的，神經絲的表達則明顯相的減少。

**研究的建議：**

根據研究結果和文獻綜述，AhR 的調節似乎在神經性疼痛中具有潛在的地位。諸如，神經慢性壓傷之類的外部刺激會增加受傷神經中 AhR 的表達，而 AhR 的配體(奧美拉唑)可以減輕這種損傷。看來 AhR 配體具有治療神經性疼痛的潛在價值。

**關鍵詞：**芳烴受體，神經性疼痛，奧美拉唑

**Purpose:**

Neuropathic pain is well-known for a damage involved in the somatosensory system, and is usually defined as pain initiated or caused by a primary lesion or dysfunction of the nervous system. Currently, there are no clinical therapies for the neuropathic pain treatment that act in a complete and decisive way. The aryl hydrocarbon receptor (AhR) is a protein that belongs to the PAS (Per-ARNT-Sim) family and contains a basic helix-loop-helix domain. The regulation of the expression of the AhR in the nervous system depends not only on internal stimuli, but also on external stimulation such as traumatic brain injury (TBI) or stroke. In our previous investigation, we found that there was significant alteration in inflammatory response from skin to the spinal cord as well as to somatosensory cortex in animals subjected to chronic constrictive injury. However, the regulation of AhR in the chronic constrictive nerve injury model has not been determined.

**Material and methods:**

In this study, we used the nerve explants culture and the chronic constrictive nerve injury model in wild or AhR knock-down mice to investigate the role of AhR expression in the nerve system and also used a AhR ligand, omeprazole, to assess its therapeutic effect on the development of neuropathic pain. There were three aims in this study. First, we assessed the effect of AhR knock down or AhR ligand in the nerve degeneration and oxidative stress in the nerve explants culture. Second, we evaluated the neurobehavior and electrophysiology in animal with AhR knock-down and also subjected to omeprazole treatment. Third, we measured the effect in the histomorphology alteration or associated protein expression regulated by the AhR.

**Results:**

In nerve explants culture, AhR knock down increased the ovoid number and omeprazole rescued the degeneration in wild or AhR (+/-), but there was no effect on the AhR (-/-). In the mechanic allodynia and thermal hyperalgesia test, either AhR (+/-) or AhR (-/-) predisposed to the hypersensitivity of pain. The somatosensory evoked potential also demonstrated that AhR knock down increased the electrical potential. The muscle weight also showed the remarkable decrease in AhR (+/-) or AhR (-/-). The significantly high expression of AhR in the wild type was noted in injured nerve, but there was no response in AhR (-/-) and subtle increase in AhR (+/-). In the histomorphology analysis, AhR (+/-) and AhR (-/-) showed the significant expression of CD 68, NGFR and TNF- $\alpha$  and the reciprocally decrease in neurofilament.

**Conclusion:**

Based on the preliminary data and the literature review, the regulation of AhR seems to play a potential role in the neuropathic pain. The external stimuli such as chronic constrictive nerve injury augments the expression of AhR in the injured nerve and the AhR agonist omeprazole could reduce this damage. It seems that AhR agonist could be a potential indication for the treatment of neuropathic pain.

**Keywords :** Aryl hydrocarbon receptor, neuropathic pain, Omeprazole

#### 利用深度學習方法，開發異常心肺音區段偵測與辨識系統

A detection and classification system for abnormal cardiac lung sounds by using deep learning methods

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醫生以聽診器方式聽診，得知心血管疾病或肺炎感染往往是第一線醫療人員，最直接與便利的方法，如何於一長串的心肺音訊號裡，發現異常的音段，成為醫生訓練養成教育的重要課題。現有公開的心音資料庫中的心音訊號標籤資料，僅針對整體原始心肺音訊號，標示為正常或異常，未對於特定的異常音段作進一步的標示，因此訓練分類器時，往往輸入錯誤的資料，而導致辨識器訓練偏差，進而影響到後續的辨識結果，因此正確標示異常音段，給予正確的標籤，為本研究的重要目標。

發展異常心音判斷的分類器時，必須面對異常資料收集不易與資料量不平衡的問題，即是異常心音數量較正常心音資料少，且需專業人員逐段標示，造成機器學習模型成效不彰，本研究以非監督式學習技術建立正常心音模型，再進行正常與異常資料測試，標記異常音段位置，本系統分為兩個部分，首先，先利用深度學習技術，將錄製的心音訊號(PCG)切割成數個完整心跳週期(包含四個狀態)，其次，再利用非監督式學習技術，僅收集正常的心音訓練資料，建立正常心音的模型，而在測試時，分別輸入正常與異常的心音資料，進行每一個週期的正常或異常判斷，最後再根據投票的結果，決定該筆心音訊號是否為異常心音。

**關鍵詞:**心肺音、訊號切割、梅爾頻率倒譜係數、非監督式學習、監督式學習、深度學習

Doctors always use the stethoscopes to listen the patients' heart or lung sounds to determine which cardiopulmonary diseases the patients get. It is an effective method to judge the possible diseases by listening the cardiac or lung sounds. Listening the cardiac or lung sound is the basic training course for medical college students. Now, the normal or abnormal labels have been manually marked for the whole recorded signals in twenty seconds to several minutes in the public datasets. The classifiers are trained by the small segmented heart cycle signals using the labels of the whole recorded signals. However, the labels of segmented cycle signals are not the same within a whole recorded signal. i.e., abnormal heart cycles seldom exist for the healthy subject, and the abnormal cycles do not always appear for the patients.

The classifiers are not well trained because the segments with incorrect labels. This will impact the classification results. In this project, we developed an unsupervised training algorithm for detecting the abnormal segments. First, the whole recorded signals are segmented into several heart cycles by using the deep learning networks. The features are next extracted and trained using the unsupervised training method, i.e., only the signals with the normal labels are trained. After that, the trained classifier will determine if patients' heart sound cycles are normal or not. The classified labels will be labelled on the original recorded signals to provide the useful information in diagnosis.

**Keywords** : Cardiac/Lung Sound, Mel-Frequency Cepstral Coefficients(MFCC), Signal Segmentation, Supervised/Unsupervised Learning, Deep Learning