臺中榮民總醫院
Taichung Veterans General Hospital

臺中榮民總醫院一一一年度與中區各大學院校合作研究計畫

111年度臺中榮民總醫院暨中區各大學院校合作研究計畫成果

聯合成果發表會

院址：407219台中市西屯區台灣大道四段1650號
電話：04-23592525　傳真：04-23595046
網址：https://www.vghtc.gov.tw/

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、弘光科技大學、東海大學、國立中興大學、國立暨南國際大學、國立臺中科技大學、國立聯合大學、逢甲大學、靜宜大學

Programs and Abstracts

111 年度臺中榮民總醫院
暨中區各大學院校
合作研究計畫成果

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

111 年度
臺中榮民總醫院暨中區各大學院校合作研究計畫
聯合成果發表會

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

工作小組

召集人	臺中榮民總醫院院長	陳適安			
副召集人	臺中榮民總醫院副院長	李政鴻			
	臺中榮民總醫院醫學研究部部主任	謝育整			
中榮醫學研究部	詹聖霖	潘宏川	陳一銘	傅彬貴	江榮山	陳春榮
	李文珍	邱雲棕	李美芳	林敬恒	廖采苓	蘇國誌
	陳享民	蕭自宏	游勝傑	陳昶翰	李佳霖	陳彥如
	許碧紋					
大葉大學	賴峯民（研發長）	蔡仁傑	鄭淑惠			
中臺科技大學	朱淑珍（研發長）	江青桂	林芷蓁	林美惠		
弘光科技大學	林聖敦（研發長）	李時雨	李詠梅			
東海大學	林惠真（研發長）	顧野松(副研發長)	李亞蒴			
國立中興大學	宋振銘（研發長）	陳健尉	闕斌如	莊秀美	張法正	
國立暨南國際大學	陳皆儒（研發長）	黃裕智	龐鳳嫻			
國立臺中科技大學	王慈娟（研發長）	盧冠霖	楊其璇	黃天麒	廖皎汝	
國立聯合大學	吳芳賓（研發長）	李芊慧				
逢甲大學	何主亮（產合長）	陳錦毅（研發長）	林彩玉	嚴慧美		
靜宜大學	林智健（研發長）	吳曉華				

聯合成果發表會議程

08:00-08:30	報到				
08:30-08:40	長官致詞				
08:40-08:45	大合照				
人工智慧與智慧大數據醫療 (主持人：國立臺中科技大學資訊管理系 / 黃天麒教授)		**計畫主持人**		**計畫共同主持人**	
		單位	**姓名**	**單位**	**姓名**
08:45-08:55	應用機器學習演算法建立台灣老年人未來失能高危險群預測模組	臺中榮總急診部	朱為民	東海大學數學系/ 東海大學資工系/ 臺中榮總急診部	陳宏銘/ 楊朝棟/ 詹毓哲
08:55-09:05	通過機器學習，從心臟超音波大數據資料庫預測主動脈瓣狹窄患者的預後	臺中榮總心臟內科	林維文	東海大學數學系	黃皇男
09:05-09:15	神經內分泌瘤 Ki-67 判讀模型之落地測試及修正	國立聯合大學電機工程學系	李佳燕	臺中榮總病理檢驗部	詹以吉
09:15-09:25	以邊緣智慧技術達成高品質急救教學即時回饋	靜宜大學資訊管理學系	詹毓偉	臺中榮總急診部/ 東海大學資工系/ 靜宜大學資訊傳播工程學系/ 靜宜大學資訊傳播工程學系/ 臺中榮總急診部/ 臺中榮總高齡醫學中心	詹毓哲/ 楊朝棟/ 張志宏/ 蔡英德/ 胡松原/ 林承賦
09:25-09:30	Q&A				
精準醫學與遺傳基因醫學 (主持人：國立暨南國際大學應用化學系 / 傅在峰教授)		**計畫主持人**		**計畫共同主持人**	
		單位	**姓名**	**單位**	**姓名**
09:30-09:40	透明質酸修飾之靛氰綠-聚乳酸甘醇酸奈米膠囊作為診斷淋巴水腫之螢光探針	逢甲大學材料科學與工程學系	簡儀欣	臺中榮總重建整形外科	賴志昇
09:40-09:50	高尿酸血症/痛風與骨質疏鬆間其單核苷酸多型性的相關性研究	中興大學應用數學系所	施因澤	臺中榮總藥劑部/ 中山醫學大學公共衛生系	張雁霖/ 廖勇柏
09:50-09:55	Q&A				
09:55-10:10	中場休息				
慢性病管理與醫院管理 / 高齡醫學、長期照顧與精神醫學 (主持人：弘光科技大學健康事業管理系(所) / 陳亮汝副教授)		**計畫主持人**		**計畫共同主持人**	
		單位	**姓名**	**單位**	**姓名**
10:10-10:20	非侵葡萄糖濃度量測方法	國立聯合大學機械工程學系	潘國興	臺中榮總研究部	陳享民
10:20-10:30	蛻皮激素訊號透過微型核醣核酸 let-7-Complex 調節嗅覺感覺神經元影響雄性果蠅同性偏好的求偶行為	國立暨南大學應用化學系	傅在峰	臺中榮總精神部	林志堅
10:30-10:40	紅藜對肌少症與相關調控分子機制之影響	靜宜大學食品營養學系	詹吟菁	臺中榮總新陳代謝科	李奕德
10:40-10:45	Q&A				
10:45-12:00	壁報展示(第一場)				
12:00-13:00	午餐				

癌症醫學 (主持人：東海大學化學工程與材料工程學系/顧野松教授)		計畫主持人		計畫共同主持人	
		單位	姓名	單位	姓名
13:00-13:10	螯合劑-抗體比於 89Zr-DFO*-labeled Anti-PD-L1 Antibody 之影響	中臺科技大學醫學影像暨放射科學系	黃蜂運	臺中榮總核醫科	蔡世傳
13:10-13:20	PAX3 在臺灣神經膠質瘤中的複製壓力與抗藥性關係探討	臺中榮總神經外科	沈炯祺	中興大學分子生物學研究所	楊文明
13:20-13:30	新型光驅動藥物與紫杉醇之協同作用：經由基因調控喚醒免疫系統治療轉移性黑色素瘤	中興大學生醫工程研究所	王惠民	臺中榮總整合性癌症中心	李旭東
13:30-13:40	探討香杉芝萃取物經由抑制 STAT3 活化而影響攝護腺癌細胞的上皮間葉轉變及癌幹特性	中興大學生命科學系	林赫	臺中榮總核醫科	王心怡
13:40-13:45	Q&A				
心血管代謝疾病與過敏免疫 (主持人：國立中興大學生物醫學研究所 / 闕斌如教授)		計畫主持人		計畫共同主持人	
		單位	姓名	單位	姓名
13:45-13:55	探討北蟲草應用於抗過敏性皮膚炎之分子機轉	大葉大學生科中心	吳建一	臺中榮總醫學研究部	李美芳
13:55-14:05	探討黑蒜萃取物改善肥胖相關過敏性呼吸道發炎之功效與機制研究	大葉大學藥用植物與保健學系	蔡仁傑	臺中榮總骨科部	曾崇育
14:05-14:15	芳基烴受體調節高遷移率族蛋白在內皮細胞和糖尿病動物模型機轉性探討	中興大學生物醫學研究所	許美鈴	臺中榮總新陳代謝科	王俊興
14:15-14:20	Q&A				
神經肌肉骨骼與 3D 列印 / 新興感染症 / 再生醫療研究 / 其他前瞻創新研究 (主持人：中臺科技大學研究發展處 / 朱淑珍研發長)		計畫主持人		計畫共同主持人	
		單位	姓名	單位	姓名
14:20-14:30	探討不同 3D 列印製程對於植牙手術導板影響	東海大學工工系	葉家宏	臺中榮總口腔醫學部	黃良吉
14:30-14:40	探索潛力 TMPRSS2 抑制劑針對抗 covid-19	靜宜大學資訊工程學系	唐傳義	臺中榮總醫學研究部	陳春榮
14:40-14:50	台灣藜對於經 IL-1b 刺激產生發炎症狀的軟骨細胞其功能性分析	國立聯合大學化學工程學系	陳郁君	臺中榮總病理檢驗部	陳志榮
14:50-15:00	利用脈衝雷射的光分解作用下在多孔矽表面生長金/二氧化鈦奈米材料於光誘導表面增強拉曼光譜學應用	國立暨南大學應用材料及光電工程學系	蕭桂森	臺中榮總兒童外科	周佳滿
15:00-15:05	Q&A				
15:05-15:20	中場休息				
15:20-16:30	壁報展示(第二場)				
16:30-	賦歸				

目錄

成果報告摘要

榮弘計畫

TCVGH-HK1118001 **探討短鏈脂肪酸的巨噬細胞/微神經膠細胞極化作用**

P23

陳春榮 臺中榮民總醫院研究部/研究員
王文綺 弘光科技大學護理系/副教授
廖素蘭 臺中榮民總醫院研究部/副技師
洪鈺婷 臺中榮民總醫院研究部/研究助理
黃瑋琪 中興大學獸醫系/博士生*
陳文英 中興大學獸醫系/教授#

TCVGH-HK1118002 **組織適配、職場靈性、個人靈性與心理健康之關係研究**

P25

張振傑 弘光科技大學健康事業管理系/助理教授
江榮山 臺中榮民總醫院醫學研究部/主任
張美玉 臺中榮民總醫院護理部/部主任
溫美蓉 臺中榮民總醫院護理部/副主任

TCVGH-HK1118003 **不同尺寸真空吸引器在生產時對於新生兒頭部的生物力學影響**

P26

蘇國誌 臺中榮民總醫院醫學研究部/副研究員
常閎智 弘光科技大學生物醫學工程系/助理教授
陳郁琪 弘光科技大學生物醫學工程系/助理教授

TCVGH-HK1118004 **基因–環境互動與早產兒母親之健康與親職效能**

P27

李時雨 弘光科技大學護理系/教授
陳永娟 中榮護理部/督導長
黃雅芳 弘光科技大學護理系/助理教授

TCVGH-HK1118005 **青少年憂鬱症與非憂鬱症個案之唾液皮質醇、α-澱粉酶與知覺壓力、憂鬱及焦慮之相關研究**

P29

林美伶 弘光科技大學護理系(所)/助理教授
黃惠美 台中榮民總醫院護理部/督導長
劉珈倩 台中榮民總醫院精神醫學部/主治醫師
黃芳亮 台中榮民總醫院兒童醫學中心/主治醫師
趙玉良 趙玉良身心醫學診所
梁鈴玉 龍井國中學校/護理師
吳郁嫻/濮采婕 弘光科技大學護理系/學生

TCVGH-HK1118006 **人工生殖輔助技術之子代健康與子癲前症關聯性**

P31

張聰民 弘光科技大學化妝品應用系/特聘教授
宮曉帆 台中榮民總醫院/主治醫師
黃惠美 台中榮民總醫院護理部/督導長
梁巧欣 弘光科技大學/研究助理

TCVGH-HK1118007 **建立急性醫療與長照服務接軌之服務平台：從出院準備服務標的族群、服務使用模式與績效探討**

P33

陳亮汝 弘光科技大學健康事業管理系/副教授
鄧喬鳳 臺中榮民總醫院護理部/督導長
黃文靈 弘光科技大學健康事業管理系/研究助理
陳思廷 弘光科技大學健康事業管理系/研究生

TCVGH-HK1118008 **運動對糖尿病足部潰瘍傷口癒合成效探討**

P35

廖怡珍 弘光科技大學護理系/助理教授
呂俊德 臺中榮民總醫院重建整形外科/主治醫師
黃明絹 臺中榮民總醫院護理部/護理師

TCVGH-HK1118009 **ADHD 兒童之基因分型及其主要照顧者親職壓力之探討**

P37

黃雅芳 弘光科技大學護理系/助理教授
黃惠美 台中榮民總醫院護理部/督導長
林志堅 台中榮民總醫院精神部兒童青少年精神科/主任
濮采婕 台中榮民總醫院/研究助理

榮東計畫

TCVGH-T1117801 **具可解釋性之X光檢測機器學習模型**

P39

陳仕偉 東海大學資工系/助理教授
蔡志文 臺中榮民總醫院放射線部/部主任
蔡清欉 東海大學資工系/教授
陳俊凱 國立陽明交通大學資工所/研究生

TCVGH-T1117802 **探討合成胜肽之抗異位性皮膚炎功效（III）**

P41

龍鳳娣 東海大學化學系/教授
李美芳 台中榮民總醫院醫學研究部/副研究員
朱裕文 台中榮民總醫院藥劑部/科主任
林靜君 東海大學化學系/博士生

TCVGH-T1117803 **應用機器學習演算法建立台灣老年人未來失能高危險群預測模組**

P43

朱為民 台中榮民總醫院家庭醫學部/科主任
陳宏銘 東海大學數學系/系主任
楊朝棟 東海大學資工系/教授
詹毓哲 台中榮民總醫院急診醫學部/科主任

TCVGH-T1117804 **探討不同 3D 列印製程對於植牙手術導板影響**

P45

葉家宏 東海大學工業工程與經營資訊學系/副教授
黃良吉 臺中榮總牙髓暨牙周病科/科主任
吳佩蓁 東海大學工業工程與經營資訊學系/研究生

TCVGH-T1117805 **MAST1 的調控機制與放射線治療應用**

P46

周佩玉 東海大學健康與運動學程/助理教授
游惟強 臺中榮民總醫院放射腫瘤部/部主任、主治醫師

TCVGH-T1117806 **通過機器學習，從心臟超音波大數據資料庫預測主動脈瓣狹窄患者的預後**

P47

林維文 心臟血管中心心衰竭科/主任
黃皇男 東海大學應用數學系/理學院院長，教授
陳宏銘 東海大學應用數學系/教授

TCVGH-T1117807 **胸痛病人表情聲調偵測系統及臨床應用之研究**

P49

楊朝棟 東海大學資訊工程學系/終身特聘教授
詹毓哲 臺中榮民總醫院急診部/科主任
林子傑 臺中榮民總醫院急診部/部主任
陳儀軒 臺中榮民總醫院急診部/總醫師
陳秀麗 臺中榮民總醫院急診部/副護理長
廖祐筠 東海大學資訊工程學系/研究生
郝曼伶 東海大學資訊工程學系/研究生

TCVGH-T1117808 **VR 應用於兒童心導管手術與心臟超音波檢查之焦慮與疼痛**

P50

謝佩珊 東海大學企業管理學系/助理教授
莊傑貿 台中榮民總醫院兒童心臟科/主治醫師
姜琇森 國立臺中科技大學資訊管理學系/教授
林韋伶 東海大學企業管理學系/碩士生

TCVGH-T1117809 **創建基於網路本體語言的人工智慧系統以支持頑固局部型癲癇的診斷與手術評估**

P52

周育誠 台中榮總神經醫學中心兒童神經外科/主任
黃欽印 東海大學工學院/院長
董欣 台中榮總神經醫學中心（內科）/主治醫師
潘思延 台中榮總神經醫學中心（外科）/主治醫師
江國樑 光田綜合醫院兒科/主治醫師
楊怡津 台中榮總神經醫學中心/研究助理

榮科計畫

TCVGH-NTCNC1118501　　臨床護理人員壓力源建模與分析-以急診部門為例

P54

陳大仁	國立臺中科技大學
徐菀雲	臺中榮民總醫院
李雅婷	國立臺中科技大學
葉月珍	國立臺中科技大學
翁愷琪	國立臺中科技大學
戴于婷	國立臺中科技大學
劉輝煌	國立臺中科技大學
林家彰	國立臺中科技大學
陳韋志	國立臺中科技大學

TCVGH-NTCNC1118502　　人工智慧協助大腸切片診斷

P55

李欣倪	臺中榮總病理檢驗部/主治醫師
盧冠霖	國立臺中科技大學中護健康學院護理科/教授
林文彥	國立臺中科技大學資訊流通學院資訊管理系/助理教授
林正堅	國立臺中科技大學資訊流通學院資訊管理系/院長
吳孟玲	成功大學/碩士生

榮逢計畫

TCVGH-FCU1118201 **利用AI卷積神經網路分析異常腸鳴音訊號-以腹腔外科手術後評估診斷為例**

P57

王坤卿 逢甲大學機械與電腦輔助工程學系/教授
沈靜慧 臺中榮民總醫院麻醉部/部主任
蔡鈺鼎 逢甲大學精密系統設計學士學位學程/學程主任

TCVGH-FCU1118202 **利用靜電紡絲技術製備奈米纖維於5-氟尿嘧啶之藥物釋放**

P59

張育誠 逢甲大學材料科學與工程學系/特聘教授
周佳滿 台中榮民總醫院外科部/主任
石長青 逢甲大學材料科學與工程學系/研究生
邱台意 逢甲大學材料科學與工程學系/專題生

TCVGH-FCU1118203 **探討慢性阻塞性肺病、空氣污染與基因對心血管疾病的相關性探討**

P60

周天穎 逢甲大學土地管理學系/教授
程建祥 臺中榮民總醫院呼吸治療科/主治醫師
廖勇柏 中山醫學大學公共衛生學系(所)/教授
辜文元 逢甲大學都市計畫與空間資訊學系/助理教授
徐書儀 中山醫學大學公共衛生學系(所)/研究助理
劉紋秀 中山醫學大學公共衛生學系(所)/研究助理
陳霈芯 中山醫學大學公共衛生學系(所)/研究助理
陸玟諭 中山醫學大學公共衛生學系(所)/研究助理
鍾季涵 中山醫學大學公共衛生學系(所)/研究助理

TCVGH-FCU1118204 **透明質酸修飾之靛氰綠-聚乳酸甘醇酸奈米膠囊作為診斷淋巴水腫之螢光探針**

P62

簡儀欣 逢甲大學材料科學與工程學系/副教授
賴志昇 台中榮民總醫院整形外科/主治醫師
馮金星 台中榮民總醫院整形外科/醫事技術師
黃偉任 逢甲大學材料科學與工程學系/碩士班
管宜君/楊舒婷/戚庭禎 逢甲大學材料科學與工程學系/大學部

TCVGH-FCU1118205 **人工智慧技術用於未閉導管的血流動力學變化辨識系統**

P64

蔡鈺鼎	逢甲大學精密系統設計學士學位學程/副教授兼主任
林明志	兒童醫學中心/主任
王坤卿	逢甲大學機械與電腦輔助工程學系/教授
黃立誠	逢甲大學電聲學程/研究生(實驗內容撰寫)
李宗毅	逢甲大學電聲學程/研究生(圖文內容撰寫)
宋汶翰	逢甲大學電聲學程/研究生(部分內容撰寫)
林珀攸	榮總(數據彙整)
王德明	榮總/醫師(醫學數據分析)
許雅淇	榮總/醫師(醫學數據分析)
徐仲庭	榮總/醫師(醫學數據分析)
林怡瑄	榮總/醫師/(醫學數據分析)

TCVGH-FCU1118206 **兒童早期療育評估與機構篩選優化**

P66

蔡耀德	逢甲大學國際經營與貿易學系/副教授
李友淳	台中榮民總醫院復健科/醫師
翁紹仁	東海大學工業工程與經營資訊學系/教授
陳誌皜	東海大學工業工程與經營資訊學系/博士生
莊友廷	東海大學工業工程與經營資訊學系/工程師

榮葉計畫

TCVGH-DYU1118301 **探討北蟲草應用於抗過敏性皮膚炎之分子機轉**

P67

吳建一 大葉大學藥用植物與食品保健學系/教授
李美芳 臺中榮總研究部/副研究員
朱裕文 臺中榮總藥學部調劑科/主任

TCVGH-DYU1118302 **以基因轉殖斑馬魚研究內酰胺酶基因(blaOXA)作用機制分析平台之建立**

P69

黃尉東 大葉大學生物醫學系/副教授兼系主任
曾建豪 台中榮民總醫院感染科/主治醫師
楊明泓 大葉大學生物醫學系/大學部學生
蔡雨潔 大葉大學生物醫學系/大學部學生
程媵雅 大葉大學物醫學系/大學部學生

TCVGH-DYU1118303 **探討樹豆根酒精萃取物於角質細胞共同培養模式之抗發炎和抗菌活性**

P71

朱裕文 臺中榮總藥學部調劑科/主任
李美芳 臺中榮總研究部/副研究員
宋祖瑩 大葉大學藥用植物與食品保健學系/教授

TCVGH-DYU1118304 **探討黑蒜萃取物改善肥胖相關過敏性呼吸道發炎之功效與機制研究**

P73

蔡仁傑 大葉大學藥用植物與食品保健學系/副教授
曾崇育 臺中榮民總醫院骨科部/主任
陳煜昌 大葉大學藥用植物與食品保健學系/專題生
陳瑀翔 大葉大學藥用植物與食品保健學系/專題生
甘絜瑄 大葉大學藥用植物與食品保健學系/專題生

榮暨計畫

TCVGH-NCNU1117901 **蛻皮激素訊號透過微型核醣核酸 let-7-Complex調節嗅覺感覺神經元影響雄性果蠅同性偏好的求偶行為**

P74

傅在峰	國立暨南大學應用化學系暨生物醫學碩士班/教授
林志堅	臺中榮民總醫院精神部/主任
蔡榮宗	國立暨南大學應用化學系/博士後研究員
劉柏廷	國立暨南大學應用化學所/博士生
洪詩純	國立暨南大學應用化學所/碩士生

TCVGH-NCNU1117902 **利用脈衝雷射的光分解作用下在多孔矽表面生長金/二氧化鈦奈米材料於光誘導表面增強拉曼光譜學應用**

P76

蕭桂森	國立暨南國際大學應用材料及光電工程系/教授
周佳滿	台中榮總小兒外科/主任
黃勝揚	台中榮總小兒外科/醫師
朱智謙	中山醫學大學醫學應用化學系/教授
王秉彥	台灣彰化基督教醫院外科部/主任兼主治醫師
廖素鈺	國立暨南國際大學電機工程學系/博士班學生
高唯甯/李宜真/龔郁涵/魏沛晴/謝佑軒	國立暨南國際大學應用材料及光電工程系/學士班學生

TCVGH-NCNU1117903 **子宮內膜癌MMR缺失之臨床病理特性及腫瘤浸潤性淋巴細胞之預後價值及免疫機轉研究**

P77

呂建興	臺中榮總婦女醫學部/婦科主任兼任副部主任
傅在峰	國立暨南大學應用化學系/教授
范鈞婷	臺中榮總婦女醫學部/住院醫師

榮臺計畫

TCVGH-CTUST1117701 **COVID-19疫情對透析患者心理健康之影響**

P79

陳呈旭	臺中榮民總醫院腎臟科/主任
葉德豐	中臺科技大學醫療暨健康產業管理系/副教授
鍾牧圻	臺中榮民總醫院腎臟科/主治醫師
何玉瑛	臺中榮民總醫院洗腎室/護理長
張靜宜	臺中榮民總醫院洗腎室/護理師
蕭菁菁	臺中榮民總醫院洗腎室/護理師
陳丁進	中臺科技大學醫療暨健康產業管理系/碩士研究生
楊宜芳	中臺科技大學醫療暨健康產業管理系/碩士研究生

TCVGH-CTUST1117702 **聚乙二醇–AuNΠ納米複合材料評價間充質乾細胞的生物相容性和分化能力**

P82

楊孟寅	臺中榮民總醫院神經醫學中心/主任醫師
劉百栓	中臺科技大學醫學影像暨放射科學系/教授
洪慧珊	中國醫藥大學醫學院生物醫學研究所/副教授
楊怡津	臺中榮民總醫院神經醫學中心

TCVGH-CTUST1117703 **螯合劑-抗體比於89Zr-DFO*-labeled Anti-PD-L1 Antibody之影響**

P84

黃蜂運	中臺科技大學醫學影像暨放射科學系/助理教授
蔡世傳	台中榮民總醫院核子醫學科/主任
龔瑞英	台中榮民總醫院核子醫學科/醫事放射師

榮興計畫

TCVGH-NCHU1117601 **基於深度學習之腎臟病理影像腎絲球分割與型態分類**

P85

莊家峰	國立中興大學電機工程學系/特聘教授
莊雅雯	臺中榮民總醫院腎臟科/主治醫師
林冠彣/陳彥伯/陳偉軒	國立中興大學電機工程學系

TCVGH-NCHU1117602 **在細胞及活體中探討imiquimod誘導黑色素生成的分子機制**

P86

謝政哲	中興大學生物醫學研究所/教授
陳怡如	臺中榮民總醫院內科部/主任
李政宜	中興大學生物醫學研究所/博士候選人

TCVGH-NCHU1117603 **甘胺酸N-甲基轉移基因表達與抗葉酸免疫調節藥物甲氨蝶呤交互影響胞內代謝之動態平衡之研究**

P88

蔣恩沛	中興大學食生系/終生特聘教授
陳一銘	中榮免疫風濕科/醫師
蘇雅麗	中興大學食生系/博士後研究員

TCVGH-NCHU1117604 **以配體蛋白結合分析法探討腫瘤蛋白 ENOX2 做為新穎抗癌藥物之蛋白標靶及其在大腸癌症治療之應用**

P90

闕斌如	國立中興大學生醫所/教授
陳周斌	臺中榮民總醫院外科部/部主任
伊斯堤	國立中興大學生醫所/博士班學生
邱詩涵	國立中興大學生醫所/碩士班學生

TCVGH-NCHU1117605 **評估肌肉注線粒體對神經擠壓傷後的神經和肌肉再生的可能性**

P92

蘇鴻麟	中興大學生命科學系/教授
潘宏川	臺中榮總醫學研究部/科主任

TCVGH-NCHU1117606 **研究丹參酚酸B鎂鹽對肥胖性肌少症之保健功效及其可能分子機轉**

P94

陳文英 國立中興大學獸醫學系所/教授
吳志成 臺中榮民總醫麻醉部疼痛科/科主任
黃瑋琪 國立中興大學獸醫學系所/博士生
賴宛平 國立中興大學獸醫學系所/碩士生

TCVGH-NCHU1117607 **PAX3 在臺灣神經膠質瘤中的複製壓力與抗藥性關係探討**

P95

沈炯祺 中榮神經外科/主任
楊文明 興大分子生物所/教授
吳慈華 興大分子生物所/助理
趙孟秦/劉維新/侯帛邑 興大分子生物所/兼任助理

TCVGH-NCHU1117608 **探討家禽里奧病毒調控癌細胞株之細胞激素及 immune checkpoint 及Toll-like receptors**

P97

劉宏仁 國立中興大學分子生物學研究所/終身特聘教授兼執行長
廖采苓 台中榮民總醫院醫學研究部/研究員
吳怡瑩 中興大學博士後/研究員
黃韋儒 中興大學博士後/研究員
李俊毅 中興大學博士班/研究生

TCVGH-NCHU1117609 **能量代謝訊息路徑對於急性淋巴性白血病之治療潛力機制探討**

P99

黃芳亮 臺中榮民總醫院兒童醫學中心血液腫瘤科/科主任
李龍緣 國立中興大學生命科學系/副教授
李佳玲 臺中榮民總醫院兒童醫學中心/博士後研究員

TCVGH-NCHU1117610 **芳基烴受體調節高遷移率族蛋白在內皮細胞和糖尿病動物模型機轉性探討**

P100

許美鈴 國立中興大學生物醫學研究所/終身特聘教授
王俊興 台中榮總新陳代謝科/主治醫師
邢相媛 國立中興大學生物醫學研究所/研究助理

TCVGH-NCHU1117611 **新型光驅動藥物與紫杉醇之協同作用：經由基因調控喚醒免疫系統治療轉移性黑色素癌**

P102

王惠民 國立中興大學生醫工程研究所/教授
李旭東 臺中榮總整合性癌症中心/主任

TCVGH-NCHU1117612 **高尿酸血症/痛風與骨質疏鬆間其單核苷酸多型性的相關性研究**

P103

施因澤 國立中興大學應用數學系(所)/教授
張雁霖 臺中榮民總醫院藥劑部/藥師
廖勇柏 中山醫學大學公共衛生學系(所)/教授

TCVGH-NCHU1117613 **特異性促消退因子在抗磷脂抗體症候群致病機轉扮演的角色**

P104

賴建成 國立中興大學分子生物學研究所/教授
譚國棟 臺中榮民總醫院過敏免疫風濕科/主治醫師

TCVGH-NCHU1117614 **探討香杉芝萃取物經由抑制STAT3活化而影響攝護腺癌細胞的上皮間葉轉變及癌幹特性**

P106

林赫 國立中興大學生科系/特聘教授兼系主任
王心怡 台中榮總核醫科/主治醫師
Ayse Celik 中興大學生科系/研究生

TCVGH-NCHU1117615 **篩選食品潛力成分探討其對大腸直腸癌生長之影響**

P108

林金源 國立中興大學食品暨應用生物科技學系/教授
陳周誠 台中榮民總醫院大腸直腸外科/主治醫師
吳亭儀 國立中興大學食品暨應用生物科技學系

TCVGH-NCHU1117616 **以犬乳腺癌細胞模式探討蛋白質二硫鍵異構酶AGR2所調控之分泌蛋白體與腫瘤轉移的關聯**

P110

劉浩屏 國立中興大學獸醫學系(所)/副教授
楊陽生 臺中榮民總醫院血液腫瘤科/主治醫師
阮賢齊 國立中興大學獸醫學系(所)/學生

TCVGH-NCHU1117617 **製備含薑黃素與肝素之強韌型水凝膠及其應用**

P112

黃智峯 國立中興大學化學工程學系/教授

王中琦 台中榮民總醫院心臟血管外科/醫師

林鼎智 國立中興大學化學工程學系

TCVGH-NCHU1117618 **利用持續性生理監測穿戴裝置、影像人工智慧演算法及心肺復健評估發展慢性肺病之長期預測及智能照護模組**

P114

傅彬貴 臺中榮總間質性整合照護中心/主任

吳俊霖 國立中性大學資訊與工程學系/教授兼系主任

程遠揚 臺中榮總復健醫學科/主任

榮靜計畫

TCVGH-PU1118101 **以邊緣智慧技術達成高品質急救教學即時回饋**

P117

詹毓偉 靜宜大學資訊學院/副教授
詹毓哲 臺中榮民總醫院職業醫學科/主任
楊朝棟 東海大學資訊工程系/終生特聘教授
張志宏 靜宜大學資訊學院/副教授
蔡英德 靜宜大學資訊學院/教授
胡松原 臺中榮民總醫院急診部/科主任
林承賦 臺中榮民總醫院高齡醫學中心/主治醫師
詹惟臣 臺中榮民總醫院/研究助理
林彥亨 靜宜大學資訊學院/研究助理

TCVGH-PU1118102 **紅藜對肌少症與相關調控分子機制之影響**

P119

詹吟菁 靜宜大學食品營養系/特聘教授
李奕德 臺中榮民總醫院/新陳代謝科主任
廖玉惠/林思佳/黃珍琳 靜宜大學食品營養系/碩士生及大學部學生

TCVGH-PU1118103 **運用深度學習技術應用於老人危險行為偵測**

P121

張志宏 靜宜大學資訊傳播工程學系/副教授
洪哲倫 靜宜大學資訊傳播工程學系/教授
朱為民 臺中榮民總醫院急診部/主任
陳柏志 靜宜大學資訊管理學系碩士班/研究生

TCVGH-PU1118104 **探索潛力TMPRSS2 抑制劑針對抗covid-19**

P122

唐傳義 靜宜大學資訊工程學系/教授
陳春榮 臺中榮民總醫院研究部/研究員
鄭雅妮 臺中榮民總醫院研究部/研究助理
廖梓榕 臺中榮民總醫院研究部/研究助理
廖素蘭 臺中榮民總醫院研究部/副技師

榮聯計畫

TCVGH-NUU1118901 **台灣藜對於經IL-1b刺激產生發炎症狀的軟骨細胞其功能性分析**

P124

陳郁君 國立聯合大學化學工程學系/助理教授
陳志榮 臺中榮民總醫院病理檢驗部/主任
陳鈺萍 國立聯合大學化學工程學系

TCVGH-NUU1118902 **可採集下肢復健數位化資料之穿戴式裝置開發**

P126

吳有基 國立聯合大學電機工程學系/教授
韓欽銓 國立聯合大學資訊工程學系/教授
程遠揚 臺中榮民總醫院復健科/主任
黃鈺榮 國立聯合大學/博士生
江均賢 國立聯合大學/專任助理

TCVGH-NUU1118903 **神經內分泌瘤Ki-67判讀模型之落地測試及修正**

P127

李佳燕 國立聯合大學電機系/教授
詹以吉 台中榮民總醫院病理檢驗部/主任
傅景佟 台中榮民總醫院病理檢驗部/主治醫師
陳律臻 台中榮民總醫院病理檢驗部/主治醫師
王慶萍 國立陽明交通大學電機系/學生
曾鈞銅 國立聯合大學電機系/學生

TCVGH-NUU1118904 **非侵葡萄糖濃度量測方法**

P128

潘國興 國立聯合大學機械系/副教授
陳享民 臺中榮民總醫院醫學研究部/研究員
李書妤/Quoc-Thinh Dinh 國立聯合大學機械系/研究生

TCVGH-NUU1118905 **高靈敏度螢光病理診測技術之開發**

P129

林永昇 國立聯合大學化學工程學系/教授
陳志榮 臺中榮民總醫院病理檢驗部/部主任
吳俊諺/吳致緯 國立聯合大學化學工程學系/大專生

成果報告摘要

榮弘計畫

TCVGH-HK1118001

探討短鏈脂肪酸的巨噬細胞/微神經膠細胞極化作用

Effects of short chain fatty acids on macrophages/microglia polarization

陳春榮/臺中榮民總醫院研究部/研究員
王文綺/弘光科技大學護理系/副教授
廖素蘭/臺中榮民總醫院研究部/副技師
洪鈺婷/臺中榮民總醫院研究部/研究助理
黃瑋琪/中興大學獸醫系/博士生*
陳文英/中興大學獸醫系/教授#

免疫細胞運作維持生物體恆定，防止致病原入侵。過度活化異常的免疫活性，反而危害組織細胞，造成病變。腸道菌群失調的結果之一，促進免疫細胞異常，發炎細胞激素過量表現。累積的臨床發現及實驗結果顯示，腸道菌衍生代謝產物，可能是串連腸道菌群失調與免疫活化的關鍵。腸道菌群失調會降低血液短鏈脂肪酸濃度、增加糞便短鏈脂肪酸濃度。醋酸、丙酸、丁酸等短鏈脂肪酸具有細胞保護、抗氧化、抗發炎、抗癌等生物活性。M1型態促發炎免疫細胞及M2型態抑制發炎免疫細胞間的轉變，影響發炎反應變化，也是抗發炎藥物的介入標的之一。本實驗係透過RAW264.7巨噬細胞株模式，探討短鏈脂肪酸的抗發炎活性。，LPS刺激會增加P-Drp1 S616、P2X7R、P2X4R、IRF5、IRF8、H3K9me2；降低CD206、Arginase 1、P-Drp1 S637。相對的，IL-4/IL-10刺激細胞，這些免疫調節分子的變化，似乎影響不大。本實驗以Sodium Butyrate及Sodium Propionate為短鏈脂肪酸的測試藥物。LPS刺激會增加M1型巨噬細胞促發炎分子表現釋出，包括TNF- 、IL-1 、NO、cAMP。Sodium Butyrate及Sodium Propionate，都可降低LPS活化的表現釋出。以Western blot量測分析細胞內訊息分子的變化，嘗試解析短鏈脂肪酸的抗發炎作用特性。LPS刺激會增加M1型巨噬細胞及促發炎相關分子表現，包括IRF5、IRF8、P2X4R、P2X7R、H3K9me2、P-ERK、P-Drp S616；降低M2型巨噬細胞及抑發炎相關分子表現，包括CD163、Arginase 1。Sodium Butyrate及Sodium Propionate，可顯著降低LPS造成的促發炎變化。然而，對於抑發炎變化，卻不明顯。整體而言，LPS刺激會顯著誘發RAW264.7巨噬細胞朝M1促發炎型態轉變，提升促發炎分子表現釋出。對於M2抑發炎型態及抑發炎分子表現釋出，作用較弱且多樣。以Sodium Butyrate及Sodium Propionate為例，短鏈脂肪酸顯著緩解LPS誘導的M1促發炎型態轉變及促發炎分子表現釋出。對於M2抑發炎型態及抑發炎分子表現釋出方面，本實驗結果沒有發現明顯作用。進一步深入探討短鏈脂肪酸的抗發炎作用及應用，尚有許多未知的特性。急需持續性研究。

Immune cells work for the maintenance of host homeostasis and avoiding pathogen invasion. However, overwhelmed immune cell activation causes bystander damage and disease initiation. Immune cell activation and proinflammatory cytokine overproduction are

consequences of gut microbiota dysbiosis. Accumulating clinical and experimental findings suggest that gut microbiota-derived metabolites could be a link between dysbiosis and inflammation. Gut microbiota dysbiosis decrease blood levels of short chain fatty acids, while increases fecal levels of short chain fatty acids. Short chain fatty acids such as acetate, propionate, and butyrate, display numerous biological activities, including cytoprotection, antioxidant, anti-inflammation, and antitumor. Polarization switch between proinflammatory M1 type and suppressive M2 type decides inflammatory responses and acts as target for the intervention of anti-inflammatory agents. Using RAW264.7 macrophage cell model, this study aimed to investigate the anti-inflammatory actions of short chain fatty acids. LPS stimulation increased expression of P-Drp1 S616, P2X7R, P2X4R, IRF5, IRF8, H3K9me2 and decreased expression of CD206, Arginase 1, P-Drp1 S637. However, addition of IL-4/IL-10 appeared to have little effect on those regulatory molecules. Sodium Butyrate and Sodium Propionate were tested as candidates of short chain fatty acids. LPS increased expression of markers related to macrophage M1 polarization and pro-inflammatory cytokine expression, including TNF- , IL-1 , NO, cAMP. Sodium Butyrate and Sodium Propionate all alleviated the expression of those molecules. The anti-inflammatory details were explored via Western blot analysis. LPS increased expression of macrophage M1 polarization- and pro-inflammation-related molecules, including IRF5, IRF8, P2X4R, P2X7R, H3K9me2, P-ERK, P-Drp S616 and decreased expression of CD163, Arginase 1 related to macrophage M2 polarization. Sodium Butyrate and Sodium Propionate had remarkable effects in alleviation of pro-inflammatory changes but displayed rare effect on anti-inflammatory changes. In conclusion, rather than macrophage M2 polarization, LPS has strong promoting effect towards macrophage M1 polarization and pro-inflammatory cytokine expression. Sodium Butyrate and Sodium Propionate showed alleviative effects mainly on macrophage M1 polarization and pro-inflammatory cytokine expression. Although current findings suggest the anti-inflammatory actions of short chain fatty acids and provide supporting biochemical evidence, the detailed anti-inflammatory mechanisms required further investigation.

TCVGH-HK1118002

組織適配、職場靈性、個人靈性與心理健康之關係研究

The relationship between fit, workplace spirituality, individual spirituality and physical and mental health

張振傑/弘光科技大學健康事業管理系/助理教授
江榮山/臺中榮民總醫院醫學研究部/主任
張美玉/臺中榮民總醫院護理部/部主任
溫美蓉/臺中榮民總醫院護理部/副主任

員工的身心健康不僅是員工個人的資產，更是組織的資產。對於醫療機構而言，員工的身心健康更是重要，它不只會造成員工的工作滿意下降、離職意願上升外，更重要的是有可能會造成病人安全的問題產生。因此，員工身心健康已是一個不可輕易忽視的議題。本計畫以正向心理學為基礎，討論個人靈性與職場靈性對身心健康的影響。同時，運用互動理論探討個人與工作適配，如何調節個人靈性與身心健康之關係；以及個人與組織適配，如何調節職場靈性與身心健康之關係。本研究採用分層隨機抽樣進行問卷調查，有效問卷為255份。研究結果顯示，個人靈性與職場靈性皆正向影響個體的身心健康，除此之外，當個人與組織適配程度越高，則職場靈性對身體健康的影響效果越強。

關鍵詞：個人靈性、職場靈性、身心健康、適配

The physical and mental health of employees is not only an individual asset, but also an organizational asset. For healthcare institutions, the physical and mental health of employees is more important. It will not only cause the decrease of employees' job satisfaction and increase of turnover intention, but more importantly, it may cause the problem of patient safety. Therefore, the physical and mental health of employees has become an issue that cannot be easily ignored. Based on positive psychology, this program explores the impact of individual and workplace spirituality on physical and mental health. At the same time, the interaction theory is used to explore how to adjust the relationship between individual spirituality and physical and mental health. And how to adjust the relationship between workplace spirituality and physical and mental health. A stratified random sampling method is used to conduct a questionnaire survey, with 255 valid questionnaires collected. The results show that both individual spirituality and workplace spirituality positively affect the physical and mental health of individuals. In addition, the higher the degree of personal and organizational fitness, the stronger the effect of workplace spirituality on physical health.

Keywords：Workplace spirituality、Individual spirituality、Physical and mental health、Fit

TCVGH-HK1118003

不同尺寸真空吸引器在生產時對於新生兒頭部的生物力學影響

Biomechanical effects of different sizes of vacuum extractors on fetal head during delivery

蘇國誌/臺中榮民總醫院醫學研究部/副研究員
常閔智/弘光科技大學生物醫學工程系/助理教授
陳郁琪/弘光科技大學生物醫學工程系/助理教授

在某些臨床情況下，一些產婦需要使用器械進行手術性陰道分娩，不同設計的真空吸引器可能會影響胎兒頭部。為了探討不同大小的矽膠吸盤萃取器對胎兒頭部的生物力學影響，本研究採用有限元分析的方法來評估。首先，我們建立了不同大小（直徑分別為40mm、50mm、60mm和70mm）、平面、半球和胎兒頭部形狀的電腦模型。本研究真空吸引器模型的形狀是半球形，使用的材料是矽膠。接下來，我們設置了1mm的真空吸引器位移和60cmHg的真空吸引器內壓力。本研究的主要觀察參數是固定端反力對真空吸引器和頭骨的von Mises應力。結果表明，直徑較大的真空吸引器會對胎兒頭部產生更大的反力、應力和應變。因此，本研究的生物力學分析結果建議臨床醫生在使用矽膠真空吸引器進行手術性陰道分娩時，應避免選擇直徑較大的真空吸引器，以減少胎兒頭部受到的外部力量、變形和相應的併發症。此外，本研究結果也為醫生在臨床實踐中提供了使用矽膠真空吸引器進行手術性陰道分娩的實用參考。

In certain clinical situations, some women may require instrumental vaginal delivery with the use of suction devices. Different designs of vacuum extractors may affect the fetal head. In order to investigate the biomechanical effects of suction cups of different sizes on the fetal head, finite element analysis was used in this study. Firstly, computer models with different sizes (diameters of 40mm, 50mm, 60mm and 70mm), flat, semi-spherical, and fetal head shapes were established. The semi-spherical shape was the main design of the vacuum extractor model in this study, and the material used was silicone. Next, a 1mm displacement of the vacuum extractor and an internal pressure of 60cmHg were set. The main observation parameters of this study were the fixed-end reaction force and the von Mises stress on the vacuum extractor and skull. The results showed that larger diameter vacuum extractors would cause greater reaction force, stress, and strain on the fetal head. Therefore, the biomechanical analysis of this study suggests that clinicians should avoid using larger diameter vacuum extractors when performing instrumental vaginal delivery with silicone vacuum extractors to reduce external forces, deformation, and related complications on the fetal head. In addition, the results of this study also provide practical reference for doctors in clinical practice using silicone vacuum extractors for instrumental vaginal delivery.

TCVGH-HK1118004

基因-環境互動與早產兒母親之健康與親職效能

Gene-environment interaction, health, and parenting efficacy among mothers with a preterm infant

李時雨/弘光科技大學護理系/教授
陳永娟/中榮護理部/督導長
黃雅芳/弘光科技大學護理系/助理教授

背景：母親並非生而平等。顯著的差異會表現在親職特徵，差異可能源自個人基因，幼兒經歷，或目前的壓力感受。然而，人們對育兒的遺傳和生物學基礎以及它們與環境因素的相互作用如何影響早期育兒知之甚少。早產發生在所有懷孕的 8-12%，眾所周知，有個住在加護病房的早產兒對媽媽來說是很有壓力的，媽媽們可能睡不好、抑鬱、極度疲憊。然而，關於母親的基因型和表型的不同如何應對壓力及影響親職知之甚少。
研究目的：1.探討母體遺傳易感性與母性親職效能的關係；2. 在激素水平上探討母體親職效能與表型易感性的關聯；3 審視睡眠為母親壓力與親職效能之間的調節因素。
研究方法：這研究包括兩個階段，使用中部某醫學中心的早產兒母親。第一階段為期7天的前瞻性自然觀察研究，使用問卷以便瞭解早產兒母親(N= 200)的壓力、睡眠、抑鬱症狀及親職的狀況。第二階段是探索性比較研究，將由前段參與研究者中招募60名母親(睡眠不良及睡眠沒問題的各半)，透過唾液來測試基因分型(COMT、DRD1、OXTR)、激素(催產素)、白介素(IL-6, IL-10)等與親職和睡眠相關的生理指標。
預期成果: 由PNI及DNA基因分型的角度，瞭解母親的情緒、睡眠、親職自我效能的影響因素。進而，為協助提升母親健康及親職能力的介入措施奠立基礎。

Background: Mothers are not all created equal. Marked individual differences are parenting behavior, which may be derived from their individual genetic makeup, childhood experiences, or current stress perception. However, little is known about the genetic and biological underpinnings of parenting and how their interactions with environmental factors may shape early parenting. Preterm births occur in 8-12 % of all pregnancies. It is well-known that to having a preterm infant hospitalized in the intensive care unit (ICU) is extremely stressful for mothers and most of others are sleep disturbed, depressed, and fatigued. However, less is known about how individual genetic makeup in mothers may moderate the effect of stress on parenting.
Research Purpose: 1. To investigate the association of maternal genetic susceptibility with parenting efficacy; 2. To explore the association of maternal parenting efficacy with endophenotype susceptibility at the hormone level; 3. To examine maternal sleep as a moderator in the association between maternal stress and parenting efficacy.
Research Method: This study includes two phases, using mothers of preterm infants from a medical center in Centra Taiwan. Phase I is a 7-day prospective, naturalistic observation

study using questionnaires to comprehend maternal stress, sleep, depressive symptoms, and parenting status of mothers (N= 200) with a preterm infant hospitalized in the ICU. Phase II is an exploratory comparative study. 60 mothers (30 impaired sleeper and 30 optimized sleepers) will be recruited from the participants in the phase I, and DNA genotyping (COMT, DRD1, OXTR) hormones (oxytocin) and interleukins (IL-6, IL10) will be tested through saliva to compare the differences of selected biomarkers related to sleep and parenting.

Anticipate Outcomes: From the perspective of PNI and DNA genotyping to understand the influencing factors of maternal mood, sleep, and parenting efficacy. Furthermore, it lays the foundation for intervention to improve the mother's health parenting.

TCVGH-HK1118005

青少年憂鬱症與非憂鬱症個案之唾液皮質醇、α-澱粉酶與知覺壓力、憂鬱及焦慮之相關研究

Correlative research on salivary cortisol, alpha-amylase and perceived stress, depression and anxiety in adolescent depression and non-depression

林美伶/弘光科技大學護理系(所)/助理教授
黃惠美/台中榮民總醫院護理部/督導長
劉珈倩/台中榮民總醫院精神醫學部/主治醫師
黃芳亮/台中榮民總醫院兒童醫學中心/主治醫師
趙玉良/趙玉良身心醫學診所
梁鈴玉/龍井國中學校/護理師
吳郁嫻/弘光科技大學護理系/學生
濮采婕/弘光科技大學護理系/學生

背景：憂鬱症為青少年常見的精神疾病之一，在成人憂鬱症個案，許多研究已經發現憂鬱症會使皮質醇(cortisol)和α-澱粉酶(alpha amylase)皆有升高的趨勢，但青少年憂鬱症個案在皮質醇和α-澱粉酶生理指標上，卻仍無定論。

研究目的：由於過去研究設計鮮少考量到性別、體重、女性初經、服藥及睡眠與自覺壓力與症狀，本研究的目的在於了解青少年憂鬱症與非憂鬱個案之唾液皮質醇、α-澱粉酶與知覺壓力、憂鬱及焦慮之相關性。

研究方法：本研究以成對病例對照研究(Pair matched case-control study)，以青少年憂鬱症個案採用年齡、性別與BMI配對1:1非憂鬱症個案，各組預定收案34人，預定收案共68人。擬採集一天四次的皮質醇和α-澱粉酶之生理指標，並收集知覺壓力量表、憂鬱與焦慮狀態等，研究將比較青少年憂鬱症與非憂鬱症個案之皮質醇和α-澱粉酶總量與斜率，並比較皮質醇和α-澱粉酶總量與斜率，以及知覺壓力量表、憂鬱與焦慮狀態的相關性與二組之間的差異。

預期成果：研究比較青少年憂鬱症與非憂鬱症個案之皮質醇和α-澱粉酶以及其知覺壓力量表、憂鬱與焦慮狀態的相關性與二組之間的差異，未來將做為補足憂鬱症青少年皮質醇和α-澱粉酶知識的缺口，並有機會作為未來介入性研究之成效指標。

關鍵詞：青少年、憂鬱症、皮質醇、α-澱粉酶

Background: Depression is one of the common mental illnesses among adolescents. In the case of adult depression, many studies have found that depression can increase both cortisol and alpha-amylase. However, adolescent depression's physiological indicators of cortisol and α-amylase in the case are still inconclusive.

Purpose: The study will compare the total amount of cortisol and α-amylase in adolescent depression and non-depression cases with The slope, and compare the total amount and slope

of cortisol and α-amylase, as well as the perceptual stress scale, the correlation between depression and anxiety, and the difference between the two groups, to fill the gap in the knowledge of cortisol and α-amylase in depressive adolescents .

Methods: A case-control study, using age, sex, and BMI to matched-pair 1:1 non-depressive patients with adolescent depression cases, 34 subjects of depression and non-depression in each group, and a total of 68 subjects are expected. This research collects the physiological indicators of cortisol and α-amylase four times daily and contains the perceived stress scale, depression and anxiety status, etc. The study will compare the total amount of cortisol and α-amylase between adolescent depression and non-depression cases and slope, and compare the total amount of cortisol and α-amylase, as well as the perceived stress scale, the correlation between depression and anxiety, and the difference between the two groups, so as to fill the knowledge of cortisol and α-amylase in adolescents with depression.

Anticipate Outcomes: The study compares cortisol and α-amylase levels, as well as perceived stress scale, depression and anxiety status, between adolescents with and without depression. The aim is to fill the gap in knowledge regarding cortisol and α-amylase levels in depressed adolescents, and to potentially serve as an effectiveness indicator for future intervention studies.

Keywords：adolescent, depression, cortisol, alpha-amylase

TCVGH-HK1118006

人工生殖輔助技術之子代健康與子癲前症關聯性

Investigate the association between Preeclampsia and Assisted Reproductive Technology (ART) pregancies based in a single medcial center in Taiwan

張聰民/弘光科技大學化妝品應用系/特聘教授
宮曉帆/台中榮民總醫院/主治醫師
黃惠美/台中榮民總醫院護理部/督導長
梁巧欣/弘光科技大學/研究助理

2019年，臺灣的生育率在200個國家中排名墊底。然而，臺灣並不孤單，不孕症影響大約15%的育齡婦女，這使得全世界有數百萬婦女遭受這不孕症所帶來的個人痛苦。高齡的婦女, 是不孕症治療問題的主要挑戰。在過去幾十年中，自1978年第一個試管嬰兒出生以來，人工生殖輔助技術（ART）得到了迅速的發展，為不孕夫婦提供了擁有完整家庭的機會。生殖醫學研究的進步不僅改變了近代的不孕症治療也改變了近代人類的歷史，人們對人工生殖輔助技術的高度需求,也提高了20世紀後期社會對人工生殖輔助技術相關醫學知識的關注度。2018年，臺灣每20個孩子中就有一個是經由人工生殖輔助技術所出生，而且隨著臺灣孕產婦年齡的增長，這出生比例是逐年上升。雖然世界上有500多萬個兒童是藉由人工生殖輔助技術所出生，其中大多數是經由試管嬰兒（體外受精）和ICSI（細胞內精子注射） 的方法，但關於人工生殖輔助技術所潛在的疑問,例如,f其操作方式是否會影響胎兒健康以及影響母體妊娠期的健康狀況仍然不清楚。子癲前症是妊產期常見的妊娠併發症，子癲前症的原因尚未完全瞭解，但子癲前症的危險因素包括試管嬰兒、高齡妊娠和多胞胎妊娠，這是在不孕症門診常見的孕婦情況。根據我們最近的研究指出, 低出生體重（LBW）、試管嬰兒、早產、先天缺陷以及透過人工生殖輔助技術所產生的妊娠的子癲前症風險是增加的。我們因此認為，有必要提出一項回顧性的研究，進一步延伸我們之前研究的結果。因此，本研究計畫案的目的是利用數據調查方法來研究人工生殖輔助技術之子代健康與子癲前症關聯性。

In 2019, the fertility rate of Taiwan appeared at the bottom of the list of 200 countries. However, Taiwan is not alone, infertility affects approximately 15% of women of reproductive age at any given time, representing, the source of much personal suffering to millions around the world. Women who postpone their childbearing age has been the major challenge for infertility concerns. In the past four decades, since the first test tube baby was born in 1978, the Assisted reproductive technologies (ART) has been rapidly developed and offering opportunities to infertility couples. The accumulation of reproductive research has changed the recent ART practices and the human history but also brought concerns into late 20 centuries as society get educated by advanced medical knowledge of ART procedures. In 2018, one in 20 children born by ART in Taiwan and the ratio is increasing by years as rising of maternal age in Taiwan get higher. Although, more than 5 million children have been born by ART

treatment, mostly by IVF (in vitro fertilization) and ICSI (intracytoplasmic sperm injection) in the world, the concerns about the potential health implications of ART as well as pregnancy condition remain unclear. Preeclampsia is a common pregnancy complication in the advanced maternal age, the cause of preeclampsia is not fully understood but the risk factors of preeclampsia including IVF, advanced age and multiple pregnancy in which are common conditions seen at fertility department. Our recent study has reported an increased risk of low birth weight (LBW), preterm birth and birth defects in IVF children, and preeclampsia in IVF mothers. We therefor believe it is important to examine this phenomenon further by proposing a study through investigating the genetic cause and the molecular mechanism underlying the case of preeclampsia. Thus, the aim of current proposal is to investigate the association between preeclampsia and well-being of ART born babies using a dry let approaches as well as genetic approach.

Keywords：In vitro fertilization (IVF), Assistant Reproductive Technology (ART), Preeclampsia

TCVGH-HK1118007

建立急性醫療與長照服務接軌之服務平台：從出院準備服務標的族群、服務使用模式與績效探討

Establish a service platform for the integration of acute medical care and long-term care services : from the target group, service use mode and performance of discharge planning from the hospital.

陳亮汝/弘光科技大學健康事業管理系/副教授
鄧喬鳳/臺中榮民總醫院護理部/督導長
黃文靈/弘光科技大學健康事業管理系/研究助理
陳思廷/弘光科技大學健康事業管理系/研究生

出院準備服務是急性與長照服務間重要的橋樑，有助於完整評估個案的照顧需求以轉介並提供長照服務，以降低家屬的焦慮，避免非計畫性的急性醫療、提升個案功能、生活品質與服務滿意度。因此從實務上制定篩選指標、釐清照顧需求及目標族群的服務使用組合模式是個重要的議題，攸關整體照顧服務體系資源的分布與耗用，故本計畫目的為探討：1.醫院臨床護理人員篩選長照個案之指標適切性、2.銜接長照服務的目標族群之特質、3.個案的醫療與長照服務使用情形與相關成效。

本研究採回溯性研究，資料以2020.10~2021.10於某醫學中心住院個案為母體，再依據研究目的篩選分析樣本，共有36,093人住院，篩選指標分數>=5分進入出院準備的個案8,378人，接受個管員出備評估有673位，持續使用長照服務363人。預計連結收案條件篩選資料、出院準備服務照會單、出院照護指導紀錄、照顧管理評估量表、醫療及長照服務使用紀錄等，以SPSS 25.0版套裝軟體進行描述性及推論性統計分析。

結果發現出院準備高風險個案的特質包含出院後有管路或呼吸器、依賴輔具或他人移動、心智功能異常、家庭照顧資源缺乏、經濟弱勢者，CMS等級偏重，將近55%為第7級以上，而在評估結果中亦可發現，85.12%的個案有接受進階照顧。有11%的出院準備個案曾發生三日內再急診，16.7%曾發生十四日再入院的狀況，女性、重大傷病、至少有一項管路或呼吸器、過去6個月曾住院、無法自行移位是重要的危險特質。照專評估時，個案近九成會持續接受服務，整體的失能等級以第四、五級居多，三日內再急診率降至8.1%，十四日內再入院也下降至13.7%，不同的人口特質在是否曾有三日內再急診、十四日內再入院並無顯著差異。

建議應讓各科別護理人員清楚篩選指標的選項與填寫原則，避免填寫重複性的問題，另可依據各類個管所需分類於資訊系統，以利後續各項服務的轉介。另針對出院後3日再急診及14日再入院高風險個案，須更聚焦在個案需求與服務間契合度，以利出院準備服務能發揮功能，協助個案順利返家照顧。

關鍵詞：出院準備、出院後3日再急診、14日再入院

The discharge planning is an important bridge between acute and long-term care services. It helps to fully assess the patient’s care needs, referrals and provide long-term care services to

reduce family caregiver's anxiety, avoid unplanned acute medical utilization, and to improve patients' physical function, quality of life, and service satisfaction. Therefore, in practice, to formulate screening indicators, clarify the needs of care and match the service, which is related to the distribution and consumption of resources of the care service system. Therefore, the purpose of this study is to explore: 1. the appropriateness of the indicators for screening long-term care cares by hospital clinical nurse, 2. the characteristics of the target group who need to connect long-term care services, 3. the patient's utilization of medical and long-term care services and its related effects.

This was a retrospective study, quantitative data was be taking the patients hospitalized in a medical center from October 2020 to October 2021 as the population, and then screening and analyzing samples according to the research purpose. It is estimated that 36,093 patients hospitalized, and 8,378 patients were screened more than 5 scores for discharge planning, and 673 people who have been evaluated by Tier-A care manager, and 363 people who continue to use long-term care services.It is expected to link the screening data of care screening, discharge planning consultation record, discharge care instruction record, care management evaluation scale, medical and long-term care service use record etc. Descriptive and inferential statistical analysis, by using IBM SPSS 25.0 statistical software, will be used to analyze the data.

It was found that the characteristics of high-risk cases for discharge planning include having a tube or ventilator after discharge, relying on assistive devices or other people to move, abnormal mental function, lack of family care resources, and economic weakness. Above, it can also be found in the evaluation results that 85.12% of the cases received advanced care. 11% of the discharge planning cases had re-admission to emergency department within 3 days, and 16.7% had re-admission to hospital within 14 days. Women, major injuries, at least one pipeline or ventilator, were hospitalized in the past 6 months, and were unable to move by themselves are important dangerous traits. According to the professional assessment, nearly 90% of the cases will continue to receive services, and the overall disability level is CMS 4 or 5. The rate of re-admission to emergency within three days has dropped to 8.1%, and the rate of readmission to hospital within 14 days has also dropped to 13.7%. There was no significant difference in demographic characteristics whether re-admission to emergency or hospital.

It is suggested that the nursing staff of each department should be clear about filling principles of the screening indicators to avoid filling in repetitive questions. In addition, they can be classified into the information system according to the needs of various case management, so as to the referral of a ppropriate services. In addition, for high-risk cases of emergency visits 3 days after discharge and high-risk re-admissions 14 days after discharge, it is necessary to focus more on the fit between the needs of the case and the service, so that the discharge planning service can be better and assist the case to return home for care.
Keywords：discharge planning, re-admission to emergency within three days, re-admissions 14 days after discharge

TCVGH-HK1118008

運動對糖尿病足部潰瘍傷口癒合成效探討

The Effect of Exercise on Wound Healing of Diabetic Foot Ulcers

廖怡珍/弘光科技大學護理系/助理教授
呂俊德/臺中榮民總醫院重建整形外科/主治醫師
黃明絹/臺中榮民總醫院護理部/護理師

研究背景:足部潰瘍是糖尿病患者的嚴重併發症,嚴重潰瘍感染時甚至可能會面臨截肢,糖尿病足部潰瘍因傷口大小、部位、嚴重程度,對有氧及抗阻力運動有活動限制。國內外文獻對於糖尿病足部運動研究較少,本研究希望將運動運用於因傷口受活動限制病人,促進潰瘍傷口癒合、穩定血糖,提升糖尿病足部潰瘍患者生活品質及降低合併症醫療成本。
研究目的:主要探討運動對糖尿病足部潰瘍傷口癒合成效。
研究方法:本研究為隨機對照研究(Randomized Controlled Trial;RCT),研究對象為中部某醫學中心整形外科糖尿病足部潰瘍病患,預計於111年1月至111年12月進行收案及資料收集,使用隨機分派表將個案分為實驗組及對照組,實驗組接受8週「勃氏運動」的介入,而對照組接受常規治療。研究測量工具共4項,包括:1.結構式問卷(含基本資料);2.Wagner潰瘍分類系統;3.糖化色素(HbA1C);4.踝肱血壓指數(ABI)。主要研究變項為傷口癒合,次要研究變項包括:糖化血色素(HbA1C)及踝肱血壓指數(ABI),於出院前、第一個月返診及第二個月返診收集兩組病人研究變項資料。
結果:已申請計畫展延,目前收案未完成,待後續收案完成後整理。

關鍵詞:糖尿病足部潰瘍、運動、隨機對照試驗

Background: Foot ulcers are a serious complication of diabetic patients. Severe ulcer infection will face amputation. Due to the size, location, and severity of the wound, diabetic foot ulcers have limitations on aerobic and resistance exercise. There are few literatures on diabetic foot exercise research at home and abroad. This study hopes to apply exercise to patients with limited wound activity, promote ulcer wound healing, stabilize blood sugar, improve the quality of life of patients with diabetic foot ulcers, and reduce medical costs for complications.
Objective: To investigate the effectiveness of exercise on wound healing of diabetic foot ulcers.
Method: This study is a randomized controlled trial (Randomized Controlled Trial; RCT). The subject is a patient with diabetic foot ulcer were recruited from plastic surgery department of a teaching hospital in Central Taiwan. Estimated to collect cases from next year January to December, Collect and use the random assignment table to divide the cases into experimental group and control group. The experimental group received 8 weeks of "Berlin Exercise" intervention, while the control group received conventional treatment. There are 4

measurement tools in the study, including: 1. Structured questionnaire (including basic information); 2. Wagner ulcer classification system; 3. Glycated pigment (HbA1C); 4. Ankle-brachial blood pressure index (ABI). The primary outcome was the wound healing, and the secondary research variables include: glycosylated hemoglobin (HbA1C) and ankle-brachial blood pressure index (ABI). The outcomes were assessed at baseline and after to discharge, and at the first and third months of return.
Result: The extension of the project has been applied for, and the current case acceptance has not been completed.

Keywords：Diabetic foot ulcer, exercise, randomized controlled study

TCVGH-HK1118009

ADHD兒童之基因分型及其主要照顧者親職壓力之探討

To explore the DNA genotypes of ADHD children and the Parenting stress of their primary caregivers

黃雅芳/弘光科技大學護理系/助理教授
黃惠美/台中榮民總醫院護理部/督導長
林志堅/台中榮民總醫院精神部兒童青少年精神科/主任暨主治醫師
濮采婕/台中榮民總醫院/研究助理

背景: 注意力不足/過動症(ADHD)是小兒心理健康門診中最常見的精神發展疾病之一，症狀包括注意力不足、過動及衝動。研究發現ADHD與神經傳導物質有關，尤其是多巴胺系統、血清素和催產素受體基因；此基因分型與ADHD相關症狀有相關性。家中有ADHD的孩童，對其主要照顧者有相當的親職壓力(parenting stress)，進而影響睡眠狀況及生活品質。

研究目的: 探討ADHD兒童之症狀及其主要照顧者之親職壓力和壓力相關症狀(例如，睡眠困擾及生活品質)之現況及相關性，並使用主觀(問卷)及客觀資料(基因分型)來探討ADHD孩童特質與主要照顧者的親職壓力相關症狀的預測因子。

研究方法: 本描述性之探索性研究，分兩階段。第一階段使用具信效度之問卷進行ADHD兒童之主要照顧者(N=300)的調查。第二階段採分層隨機取樣自第一階段的樣本群，將收集60名患孩 (其照顧者高親職壓力及低親職壓力各30名)之唾液做基因分型檢測。

預期成效: 探討ADHD兒童特質及其主要照顧者特質和睡眠困擾及生活品質對親職壓力的預測力，以作為後續介入研究之參考依據。

Background: Attention deficit/Hyperactivity disorder(ADHD) is one of the most common mental developmental disease in pediatric out-patient clinic; symptoms include attention insufficient, hyperactivity, and impulse. Studies have revealed that ADHD is related to neurotransmitter, especially dopamine system, serotonin and oxytocin receptor genes; these DNA genotypes are related to ADHD related symptoms. Having a child with ADHD may cause considerable parenting stress, which could affect the primary caregivers' sleep and quality of life.

Research Purpose: To explore the status and associations of the symptoms of ADHD children and their primary caregiver's parenting stress and stress-related symptoms (e.g., sleep disturbance and life quality). Further, to use subjective (questionnaires) and objective (DNA genotypes) data to explore the predictor for the traits of ADHD children and the parenting stress-related symptoms.

Research Method: This descriptive, exploratory research includes two phases. First phase will use psychometrics sound questionnaires to investigate the primary caregivers (N= 300) of children with ADHD. Second stage will use stratified random sampling from the participants

in first phase, and the saliva of 60 ADHD children (children will be categorized into two groups based on their primary caregivers scores) will be used to detect their DNA genotype.

Anticipate Outcomes: To explore the traits of children with ADHD and the characteristics of their primary caregivers, as well as the predictors of parenting stress-related symptoms, sleep disturbances and quality of life. Findings from this study could serve as the foundation for future intervention study.

榮東計畫

TCVGH-T1117801

具可解釋性之X光檢測機器學習模型

Explanable Machine Learning Model for X-Ray Evaluation

陳仕偉/東海大學資工系/助理教授
蔡志文/臺中榮民總醫院放射線部/部主任
蔡清欉/東海大學資工系/教授
陳俊凱/國立陽明交通大學資工所/研究生

近年來,隨著深度學習的快速發展，人工智慧逐步在醫療領域扮演重要角色。綜觀而論，人工智慧於醫療領域最主要且廣泛的應用為協助醫師快速從訊息含量大的醫療影像中,找出病患容易被忽略的初期病徵,以此即時診斷與及早治療。本研究亦是利基於深度學習技術,但將焦點著重於醫療流程的改善。根據最新一期台灣病人安全通報系統(Taiwan Patient-safety Reporting system, TPR)2020 年年報(Annual Report 2020)顯示,檢查檢驗事件為近 5 年來通報事件排名前5名的事件,而檢查檢驗的通報事件中有接近三成的比例在事件發生後會對病患的健康產生影響。病患安全是醫療服務的重要基礎,通過分析病安事件進行醫療作業流程的改善以預防及減少病患所遭受的風險、錯誤和傷害是提升病患安全的一大關鍵。

本研究在 X 光檢查流程中,提前在 X 光照射前,先行對病患患位擺位拍攝 RGB 影像,並使用卷積神經網路模型對此 RGB 影像進行影像分類任務,得到分類結果後,將其與醫囑比對是否相符,若為否,則即時發出警示提醒放射師進行擺位更正。實驗上以臺中榮民總醫院門診 X 光室所收集的資料集進行訓練及驗證,資料集涵蓋 49 個不同的類別,總訓練及驗證張數超過 12,000 張,目標希望建立一套即時的偵錯預警輔助系統,以改善醫療服務品質及提升病患安全。

With the rapid development of deep learning, Artificial Intelligence(AI) has gradually played an important role in the medical field. Among them, the most widespread application is to assist doctors to quickly find out early symptoms of patients from medical images with a large amount of information. However, this study focuses on the improvement of the medical process.

According to the latest Taiwan Patient-safety Reporting system (TPR) 2020 Annual Report, inspection incidents are among the top 5 events reported in the past five years, and nearly 30% of these incidents will have an impact on the health of the patients after the incident. Patient safety is an important foundation of medical services. It is a key to improve patient safety by improving the medical operation process through the analysis of patient safety events to prevent and reduce the risks, mistakes and injuries suffered by patients.

In this study, in the process of X-ray examination, the RGB image of the patient site was

taken in advance before the X-ray irradiation. Then the Convolutional Neural Network(CNN) model is used to perform image classification on this RGB image. After the classification result is obtained, it is compared with the doctor's order to see if they are consistent. In the experiment, the data set collected by Taichung Veterans General Hospital was used for training and testing. The data set covers 49 different categories, and the total number of training and testing sheets exceeds 12,000. The goal of this paper is to establish a real-time error detection and early warning assistant system to improve the quality of medical services and enhance patient safety.

TCVGH-T1117802

探討合成胜肽之抗異位性皮膚炎功效（III）

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

龍鳳娣/東海大學化學系/教授
李美芳/台中榮民總醫院醫學研究部/副研究員
朱裕文/台中榮民總醫院藥劑部/科主任
林靜君/東海大學化學系/博士生

異位性皮膚炎（AD）是常見的慢性過敏性皮膚病之一，其致病原因由遺傳和環境等多種因素所導致。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。抗微生物胜肽 (AMPs) 富含正電荷及疏水性胺基酸殘基，能透過物理性方式降解細菌的細胞膜，故不易使病原菌產生抗藥性。部分 AMPs能抑制脂多醣 (LPS) 所誘導的細胞因子及一氧化氮 (NO) 釋放，進而被開發成抗發炎胜肽。因此，我們選擇具有良好的抗菌活性及低溶血性的抗微生物胜肽HDM-2作為模板，並參考抗菌胜肽資料庫 (APD) 設計並合成出以中心對稱且具有不完美兩親性的 LT 系列胜肽 (LT-1 ~ LT-6)。胜肽設計策略是透過胺基酸Ile、Val、Leu的置換提高胜肽的疏水性，同時也變換胜肽對稱中心胺基酸的電荷以形成不完美的兩親結構。比對抗發炎胜肽中常見的胺基酸組成後，推測富含Leu及Arg的 LT系列胜肽可能具有抗發炎作用。本研究目的將針對 LT系列胜肽進行生物活性測試，討論胜肽對稱中心胺基酸的電荷及不完美兩親性的結構對生物活性的影響。在胜肽合成與純化後，透過蟑螂過敏原rPer 10所誘導的 HaCaT人類角質細胞平台來篩選LT系列胜肽對於AD的治療功效。結果顯示LT-1不僅顯著地抑制發炎指標IL-8、CCL-20和GM-CSF等基因的表現，且細胞毒性測定中也展現出較高的生物安全性。我們也測定LT系列胜肽針對三種細菌 (大腸桿菌、金黃色葡萄球菌及綠膿桿菌) 的抑制作用，結果顯示LT系列胜肽皆能有效抑制大腸桿菌的生長，而LT-1對大腸桿菌的最小抑制濃度約為50μg/mL。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AMPs 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 β-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。

Atopic dermatitis (AD) is one of the most common chronic allergic skin diseases, and its pathogenesis is caused by multiple factors such as genetics and environment. Keratinocytes are known to be activated by a variety of environmental stimuli and to release several

cytokines contributing to the development of AD. Antimicrobial peptides (AMPs) are rich in positively charged and hydrophobic amino acid residues, which can physically degrade bacterial cell membranes, making it difficult for pathogenic bacteria to develop drug resistance. Some AMPs can inhibit the release of cytokines and nitric oxide (NO) induced by lipopolysaccharide (LPS) and have been developed into anti-inflammatory peptides. Therefore, the antimicrobial peptide HDM-2 with good antibacterial activity and low hemolysis was selected as a template, and then LT series peptides (LT-1 ~ LT-6) with centrosymmetric and imperfect amphiphilic characteristics were designed and synthesized with reference to the antimicrobial peptide database (APD). The peptide design strategy is to increase the hydrophobicity of the peptide by substituting amino acids for Ile, Val, and Leu. At the same time, it also changes the charge of the symmetrical central amino acid of the peptide, forming an imperfect amphiphilic structure. After comparing the common amino acid composition of anti-inflammatory peptides, it is speculated that the LT series peptides rich in Leu and Arg may have anti-inflammatory effects. The purpose of this study is to evaluate the biological activity of the LT series of peptides, and discuss the impact of the charge of the symmetrical central amino acid of the peptide and the imperfect amphiphilic structure on its biological activity. After peptide synthesis and purification, the therapeutic efficacy of LT series peptides on AD was evaluated through the HaCaT human keratinocyte platform induced by the cockroach allergen rPer 10. The results showed that LT-1 not only significantly inhibited the rPer 10-activated gene expression of inflammatory indicators such as IL-8, CCL-20 and GM-CSF but also had high biological safety. We also assayed the inhibitory effect of LT series peptides against three bacteria (E. coli, S. aureus and P. aeruginosa), and the results showed that all LT series peptides effectively inhibited the growth of E. coli. The minimum inhibitory concentration of LT-1 against E. coli was about 50μg/mL. IL-8 is a representative indicator of local severity in skin lesions of AD. LT-1 was found to significantly inhibit the expression of IL-8 in Per a 10-induced HaCaT cells, even better than dexamethasone. 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 AMPs in AD skin lesions, explaining the high frequency of AD-related infections. Interestingly, LT-1 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.

TCVGH-T1117803

應用機器學習演算法建立台灣老年人未來失能高危險群預測模組

Using Machine Learning Algorithm to Establish High-Risk Group Prediction Model for Disability in Taiwan's aged population

朱為民/台中榮民總醫院家庭醫學部/科主任
陳宏銘/東海大學數學系/系主任
楊朝棟/東海大學資工系/教授
詹毓哲/台中榮民總醫院急診醫學部/科主任

背景

預測住院老年人出院後的身體功能是非常重要的。本研究旨在通過機器學習演算法，利用電子健康記錄（EHR）和周全性老年醫學評估（CGA），在臺灣住院的老年人中建立出院後身體功能的預測模型。

研究方法

資料取自臺灣中部某醫學中心的臨床資料庫。納入 2012 年 1 月至 2018 年 12 月入住急性老年病房的老年人進行分析。剔除數據缺失者。從 EHR 和 CGA 的資料中，共有 62 個臨床特徵被輸入到模型構建中。我們使用了三種不同的機器學習演算法，包括 XGBoost、隨機森林和 Logistic 回歸。

結果

共有 1,755 名老年人被納入最終分析，平均年齡為 80.68 歲。對於出院後身體功能的準確預測，XGBoost 和隨機森林模型的預測準確率均為 89%，而 Logistic 回歸的準確率僅為 33%。對於出院後身體功能的分類預測，XGBoost、隨機森林和 Logistic 回歸的預測準確率為 92%。所有 3 個模型的 auROC 都達到 98%。最重要的 3 個特徵是基礎的日常生活活動功能（ADL）、入院時的日常生活活動功能和入院時的迷你精神狀態檢查（MMSE）。

結論

結果顯示，通過機器學習模型，利用 EHR 和 CGA 的資料可以準確預測住院老年人出院時的身體功能。

關鍵字：身體功能、機器學習、老年人、人工智慧、周全性老年評估

Backgrounds

To predict physical function upon discharge among hospitalized older adults is important. This study aimed to develop a prediction model of physical function upon discharge by machine learning algorithm with electrical health records (EHR) and comprehensive geriatrics assessments (CGA) among hospitalized older adults in Taiwan.

Methods

Data was retrieved from clinical database of a tertiary medical center in central Taiwan. Older adults admitted to acute geriatric unit from Jan 2012 to Dec 2018 were included for analysis. Those with missing data were excluded. From data of EHR and CGA, total 62 clinical features

were input to model building. We used 3 different machine learning algorithm, including XGBoost, Random forest and Logistic regression.

Results

Totally 1,755 older adults were included in final analysis, with mean age of 80.68 years. For accurate prediction of physical function upon discharge, the accuracy of prediction was both 89% for XGBoost and Random forest model, while Logistic Regression was with 33% of accuracy only. For categorical prediction of physical function upon discharge, the accuracy of prediction was 92% for XGBoost, Random forest, and Logistic Regression. The auROC reached 98% for all 3 models. Top 3 features of importance were activity of daily living (ADL) of baseline, ADL during admission, and Mini mental status examination (MMSE) during admission.

Conclusions

The results showed that physical function upon discharge among hospitalized older adults can be predicted accurately during admission by machine learning model with data of EHR and CGA.

Keywords: Physical function, Machine learning, Older adults, Prediction Model, Comprehensive geriatric assessment

TCVGH-T1117804

探討不同3D列印製程對於植牙手術導板影響

Effect of Different 3D Printing Processes on Surgical Guides for Dental Implant Placement

葉家宏/東海大學工業工程與經營資訊學系/副教授
黃良吉/臺中榮總牙髓暨牙周病科/科主任
吳佩蓁/東海大學工業工程與經營資訊學系/研究生

隨著 3D 列印技術之演進與生物相容性醫療材料多元化，使得 3D 列印技術所製成的醫療器材如手術導引板相繼產生，在過去有許多研究顯示了 3D 列印光固化技術的 SLA (Stereo Lithography Apparatus)製程與 PolyJet 技術具有高度的真實性與精確度，也適合應用於醫療領域中，但植牙手術導板在臨床使用之前必須經過標準的消毒滅菌處理，當經過不同的消毒滅菌處理後，植牙手術導板是否維持相同的精度則產生了疑慮，因此本研究將深入探討 SLA 製程的 Dental SG 樹脂與 PolyJet 技術的 MED 610 樹脂，在經過四種醫院常見的消毒滅菌後之變化情形。

本研究將樹脂材料的變化分析分為外部變形與內部應力兩個部分，並依據國際標準 Tensile Properties of Plastics 規範 ASTM (American Society for Testing and Materials) D638 繪製標準試片。在外部變形部分將利用 3D 掃描儀取得標準試片消毒滅菌前後之掃描檔，並利用三維檢測軟體(GOM Inspect)進一步分析標準試片的外部變化程度。內部應力分析的部分則藉由拉伸試驗探討 Dental SG 樹脂與 MED 610 樹脂的抗拉強度，並利用有限元素分析軟體 ANSYS 做進一步的驗證。

With the evolution of 3D printing technology and the diversification of biocompatible medical materials, medical devices such as surgical guides made by 3D printing technology have been successively produced. In the past, many studies have shown that the SLA (Stereo Lithography Apparatus) process of 3D printing and the PolyJet process have a high degree of authenticity and precision. They are also suitable for use in the medical field. However, the surgical guide must undergo standard process of disinfection and sterilization before clinical use, and whether the surgical guide maintains the same accuracy after different disinfection and sterilization treatments. This study will delve into the changes in the SLA process's Dental SG resin and PolyJet's MED 610 resin after testing four common disinfection and sterilization methods in hospitals. In this study, the change analysis of resin materials is divided into two parts: external deformation and internal stress, and standard test pieces were drawn according to Standard Test Method for Tensile Properties of Plastics ASTM D638. In the external deformation section, the 3D scanner will be used to obtain the scan files before and after the standard test strip disinfection and sterilization, and the 3D inspector (GOM Inspect) is used to further analyze the external variation of the standard test strip. The internal stress analysis explores the tensile strength of Dental SG resin and MED 610 resin through the tensile test and further verification by ANSYS which is finite element software.

TCVGH-T1117805

MAST1的調控機制與放射線治療應用

The regulatory mechanism of MAST1 and application of radiotherapy

周佩玉/東海大學健康與運動學程/助理教授
游惟強/臺中榮民總醫院放射腫瘤部/部主任、主治醫師

頭頸部鱗狀細胞癌（HNSCC）是世界上最常見的癌症之一，近年來放射線治療是頭頸癌的主要治療方式,但在部份腫瘤給予放射線治療後易產生抗性問題。在化療藥物抗藥性（chemotherapy resistance）相關文獻中，Microtubule associated serine/threonine protein kinase 1（MAST1）分子被報導出具有影響性。其在 MAST1 為介導而啟動 MEK1 訊息傳遞路徑，提供抗凋亡、促進癌細胞增殖和腫瘤生長。然而，在 HNSCC 放射線治療後 c Raf 和 MEK1 是否會受到 MAST1 的影響仍有待澄清。故本篇研究的主軸將著重於在放射線後頭頸癌細胞中 MAST1 是否參與 Ras/Raf/MAPK 調控作用及相互的關係探討，以期將能協助瞭解 MAST1 的表現調控，以及在預測癌症病患對放射線治療反應好壞的生物標記。在本篇研究分析 MAST1 在病人組織的表現含量，利用 tissue arrays 分析口腔正常組織、舌癌及下咽癌檢體 MAST1 的含量，分析 tissue arrays 所提供的臨床資料以了解是否 MAST1 的表現與臨床上頭頸癌的惡性度有關。也使用人類口腔癌細胞株(SAS)來進行研究，利用西方點墨法（Western blot）分析細胞 MAST1 的表現及探討其觀察 Raf, MEK, ERK 訊息傳遞路徑是否參與在 MAST1 的作用當中，再進一步分析在輻射給予之下 Western blot 分析 MAST1 之表達量變化。

Head and neck squamous cell carcinoma (HNSCC) are one of the most common cancers in the world. In recent years, radiation therapy is the main treatment for head and neck cancer, but some tumors are prone to resistance problems after radiation therapy. Microtubule-associated serine/threonine-protein kinase 1 (MAST1) has been reported to be influential in chemotherapy resistance. It initiates the MEK1 signal transduction pathway mediated by MAST1, provides anti-apoptosis, promotes cancer cell proliferation and tumor growth. However, it remains to be clarified whether cRaf and MEK1 can be affected by MAST1 after radiotherapy in HNSCC. Therefore, the main axis of this project will focus on whether MAST1 is involved in the regulation of Ras/Raf/MAPK and the relationship between them in head and neck cancer cells after radiotherapy. The final results of this project will help us to understand the regulation of MAST1 expression as well as prognostic biomarkers for cancer patients.

TCVGH-T1117806

通過機器學習，從心臟超音波大數據資料庫預測主動脈瓣狹窄患者的預後

Predicting AS patients Prognosis From Large Echocardiography Record Datasets by Machine

林維文/心臟血管中心心衰竭科/主任
黃皇男/東海大學應用數學系理學院/院長，教授
陳宏銘/東海大學應用數學系/教授

在台灣逐漸步入老年化社會，主動脈瓣狹窄患者也隨之增加，在台中榮總心臟血管中心治療此族群患者有外科手術、吃藥控制保守治療、及經皮主動脈瓣支架置放術。心臟科醫師節根據國外文獻報導加上自己的經驗，來建議患者選擇不同的治療路徑，但是目前沒有台灣本土的資料整理及評估指標與臨床路徑。台中榮總心臟超音波室每年約有一萬人次患者接受檢查，報告參數(包括左右心房與心室的厚度與直徑，瓣膜面積與血液流速，腔室壓力等)，每位患者有 25 個參數值，加上血壓、心跳、身高、體重等生理測量值，共約三十個參數，自 103 年起皆用格式化數位儲存於心超室伺服器，並可用 excel 檔輸出，文字報告與動靜態影像亦數位化儲存，留待將來分析，目前約累積十五萬筆資料。本研究與東海大學應用數學系合作，初步分析 103-105 三年內，把主動脈狹窄患者的生理及超聲資訊為四組，分別是 Group 1:接受經皮主動脈瓣支架置放術(Transcatheter aortic valve implantation,TAVI); Group 2:吃藥控制保守治療; Group 3: 接受外科手術置換主動脈瓣膜(Surgical aortic valve replacement ,SAVR); Group 4: 未接受任何治療，進行數據預處理、分析建模、模型評價與優化，預測何種類型的患者接受何種瓣膜介入治療，對患者心臟整體結構、功能與預後最為有利。接著我們將利用此一預測模式，檢視 106-109 年心臟超音波報告，驗證預測模式並加以修正，據以提高模式的準確性。由於每年心臟超音波檢查患者不斷提升，藉由更多數據的分析，可使預測準確性不斷提升。

未來的研究我們也將加入更多生化數據，如膽固醇、血糖、尿酸等，擴大預測範圍，此一分析模式也可以使用在心血管中心其他類型疾病患者，如心肌梗塞、心率不整、節率器置放後的患者，對不同心臟疾病患者提供客制化的建議並預測未來心臟的功能。

關鍵字：主動脈瓣狹窄，心臟超音波，經皮主動脈瓣支架置放術，外科手術置換，機器學習

In Taiwan, the aging society has gradually entered, and the number of patients with aortic stenosis has also increased. The patients treated in Cardiovascular Center have several choice, including surgical procedures, conservative treatment with medication control, and percutaneous aortic valve implantation (TAVI). Cardiologists recommends patients to choose different treatment paths based on previous reports and their own experience. However, there is limited Taiwanese data for evaluation indicators and clinical pathway follows. There are 10,000 patients per year who receive echocardiography examination at cardiac ultrasound Lab. The parameters (heart chamber diameter and thickness, valve area, blood flow rate and

pressure, etc.) are recorded. Each patient has 25 parameter values. Physiological measurements such as blood pressure, heartbeat, height, weight, etc. are also stored digitally in the echocardiographic server and can be output in excel files. Text reports and ultrasound images are also digitized and store it for future analysis. Currently we accumulate about 70,000 records within 6 years. In this study, in collaboration with the Department of Applied Mathematics, Tunghai University, we analysis of aortic stenosis patients during 2014 to 2016. These patients were divided into four groups, namely Group 1: Transcatheter aortic valve implantation (TAVI); Group 2: Conservative treatment with medication control; Group 3: Surgical aortic valve replacement (SAVR); Group 4: No treatment was performed. Evaluation and optimization of models to predict which types of patients receive which valve interventions are most beneficial to the overall structure, function and prognosis of the patient's heart. Then we will use this prediction model to review the 2017-2019 cardiac ultrasound report, verify the prediction model and modify it to improve the accuracy of the model. As the number of patients undergoing cardiac ultrasound examinations continues to increase each year, the accuracy of predictions can be continuously improved through the analysis of more data. In future research, we will also add more biochemical data, such as cholesterol, blood glucose, and uric acid, to expand the prediction range. This analysis mode can also be used in patients with other types of diseases in cardiovascular centers, such as myocardial infarction, arrhythmia, and pacemaker settings. Try to provide customized advice to patients with different heart diseases and predict his cardiac function after treatment.

Keywords: aortic stenosis, echocardiography, TAVI, SAVR, machine learning

TCVGH-T1117807

胸痛病人表情聲調偵測系統及臨床應用之研究

Expression Tone Detection System for Patients with Chest pain and Clinical Application Research

楊朝棟/東海大學資訊工程學系/終身特聘教授
詹毓哲/臺中榮民總醫院急診部/科主任
林子傑/臺中榮民總醫院急診部/部主任
陳儀軒/臺中榮民總醫院急診部/總醫師
陳秀麗/臺中榮民總醫院急診部/副護理長
廖祐筠/東海大學資訊工程學系/研究生
郝曼伶/東海大學資訊工程學系/研究生

胸痛是急診就醫病患中常見的主訴，主訴中包含胸痛的病患總數，約莫佔了急診就醫總人數的三成。而在這群病人中也潛藏可能致命性的胸痛，包含急性冠心症、主動脈剝離、肺栓塞等，因此如何在病患狀況惡化到不可逆前力挽狂瀾便是急診團隊一直需要努力的課題。然而在病患到達急診後一般流程不外乎病史詢問、理學檢查、心電圖、胸部 X 光以及抽血後等待的實驗室檢驗數值，但在這些輔助診斷的工具中，卻一直缺乏有效的持續性監測方法。本研究計畫透過頻圖譜分析以及卷積神經網路模型進行訓練以及預測，來完成以表情聲調偵測系統作為胸痛病人的臨床診斷工具，以及作為即時性、持續性、非侵入性之監測。

關鍵詞：卷積神經網路、表情聲調偵測系統、頻圖譜分析、胸痛病人、非侵入性之監測

Chest pain is a common complaint among patients seeking emergency medical care, accounting for approximately 30% of all emergency department visits. Within this group of patients, there may be potentially life-threatening causes of chest pain, including acute coronary syndrome, aortic dissection, and pulmonary embolism. Therefore, how to intervene before the patient's condition becomes irreversible is always a challenge for emergency medical teams. However, the general process for patients who arrive at the emergency department usually involves taking a medical history, performing a physical examination, conducting an electrocardiogram, chest X-ray, and waiting for laboratory test results. Among these diagnostic tools, there has been a lack of effective continuous monitoring methods. This research project aims to use spectrogram analysis and convolutional neural network models for training and prediction to develop an expression tone detection system as a clinical diagnostic tool for chest pain patients, as well as a real-time, continuous, non-invasive monitoring tool.

Keywords: CNN convolutional neural network, expression tone detection system, frequency atlas analysis, chest pain, non-invasive monitoring

TCVGH-T1117808

VR應用於兒童心導管手術與心臟超音波檢查之焦慮與疼痛

Applied VR in Reducing Anxiety and Pain in Children's Cardiac Catheterization and Echocardiography

謝佩珊/東海大學企業管理學系/助理教授
莊傑貿/台中榮民總醫院兒童心臟科/主治醫師
姜琇森/國立臺中科技大學資訊管理學系/教授
林韋伶/東海大學企業管理學系/碩士生

近年來台灣在兒童醫療上人力分布不均及人力短缺，且許多兒童醫療人員在執行醫療行為時需花雙倍的時間在安撫兒童負面情緒上，導致醫療效率降低，同時增加醫療人員壓力，長期下來影響兒童醫療人力資源不足問題。因此，本研究希望透過 VR 的介入達到兒童注意力轉移的同時且能降低醫療人員壓力。

本研究對象為台中榮總兒童心臟科 4-18 歲患者，試驗過程中透過心律變異資料、AWS 人臉辨識及醫療人員的問卷增加研究的客觀性，且透過 VR 實驗組與對照組共 50 位受試者來比對 VR 是否能轉移兒童在插針上疼痛的注意力。研究結果發現 VR 的介入並沒有為兒童舒緩緊張與疼痛感，研究人員在實驗過程中的觀察推論出可能的原因為，VR 設備對於兒童來說有點太大，多數兒童在插針時會從縫隙偷看目前插針的狀況，使得注意力無法真的獲得轉移，反而導致兒童更加緊張。但是對於護理人員與家屬的壓力減緩有一些幫助，只是沒有達到顯著性差異。從 HRV 得到的結果推論兒童在插針時，有 VR 的介入，確實會比沒有使用 VR 組別的兒童，較為興奮，心跳會加快。而 AWS 判讀的結果與研究人員只有 38%的判讀結果是一致的，後續需要更多的照片進行 AWS 的機器學習與訓練，才能使得判讀結果更為準確。

本研究在學術上，能提供學者進一步了解 VR 應用於兒童插針的有效性，以及在實務上透過臨床實驗的經驗與 VR 導入，更了解注意力轉移與疼痛管理。

關鍵詞：注意力轉移、VR、AWS 人臉辨識、心律變異

In recent years, Taiwan has uneven manpower and shortage of labor in children's medical care, and many children's medical personnel need to spend double time to appease the negative emotions of children when performing medical behaviors, resulting in a reduction in medical efficiency. It affects the problem of insufficient human resources of children's medical care. Therefore, this study hopes to achieve children's attention to transition through VR intervention and reduce the pressure of medical staff.

This research object is a 4-18-year-old patient in Taichung Veterans General Hospital. To increase objectivity of the study during the experiment, we adopt HRV, AWS face recognition, and questionnaires of medical staff to test by 50 subjects of VR experiment group and the control group. The results of the study found that the intervention of VR did not soothe nervousness and pain for children. Researchers' observations in the experiment and specified that the possible cause is that VR equipment is a bit too large for children. Most children peek from the gaps when they are injected, making the attention cannot really be transferred, but the children are more nervous. However, VR intervention helps the pressure of nursing staff and

their families decreased, but it has not achieved significant differences. The results obtained by HRV, it is inferred that when children's intervention is involved in the injection, it is indeed more excited than children who do not use the VR group. The heartbeat will speed up. The results of the AWS interpretation are consistent with the researchers' results only reach 38%. In the future, more photos are required to perform AWS machine learning and training to make the judgment results more accurate.

In academic, this study can provide scholars to further understand the effectiveness of VR applications for children's injection. In practical, nursing can understand the attention transfer and pain management through VR clinical experiments in practice.

Keywords: Attention transfer, VR, AWS face recognition, heart rate variability

TCVGH-T1117809

創建基於網路本體語言的人工智慧系統以支持頑固局部型癲癇的診斷與手術評估

Creating A Web Ontology Language based AI system to support the diagnosis and preliminary

周育誠/台中榮總神經醫學中心兒童神經外科/主任
黃欽印/東海大學工學院/院長
董欣/台中榮總神經醫學中心（內科）/主治醫師
潘思延/台中榮總神經醫學中心（外科）/主治醫師
江國樑/光田綜合醫院兒科/主治醫師
楊怡津/台中榮總神經醫學中心/研究助理

目的：我們打算開發一個具有更新知識的人工智慧系統，以幫助癲癇學家更快、更準確地查明個人癲癇發作的起源。

方法：我們分析並建立了以符號學為重點的本體論知識，用於癲癇發作模式、癲癇發作描述符、腦波 描述符號、癲癇發作起源的解剖位置、癲癇發作起源的偏側化、Brodmann 區域的分類。本研究應用 Protégé 本體工具，為了使系統更貼近臨床專家的推理思維，我們對其他癲癇相關知識進行分類建構，包括心智功能、腦影像表現、癲癇手術方法等。我們使用 Ontology Web 具有描述邏輯 (OWL-DL) 和語義 Web 規則語言 (SWRL) 的語言來設計表達這些本體之間關係的規則，隨後利用 15 例代表性病例的臨床數據，對系統進行了測試

結果：我們設計了一個界面，供醫生輸入患者的各種特徵。 隨後，將 15 例代表性病例的臨床數據應用到人工智慧系統中。通過 SWRL 和推理引擎 Drool 的執行，11 例正確推斷出可能的致癇區（準確率 73.3%）。 不過，這可能僅限於患者自身的描述和病歷，但這個準確率與一般癲癇專家通過符號學判斷致癇區的準確率相當。但如果加入腦波數據進行驗證，則可正確診斷 13 例（準確率 86.7%）。

結論：我們清楚地表明我們的 人工智慧系統可以提高診斷率，未來在經過更大樣本的病例測試後，我們相信在臨床診斷的第一線利用這個人工智慧系統，可以加快診斷的確認速度，並有助於避免不必要的高成本研究。

Purpose: We intend to develop an AI system with updated knowledge to help epileptologists pinpoint the origin of individual seizures more quickly and accurately.

Methods: We analyzed and built ontology knowledge, which focuses on semiology, for the classification of seizure patterns, seizure descriptors, EEG descriptors, and seizure-originated anatomic locations, seizure-originated lateralization, Brodmann areas. Protégé ontology tool was applied in this study. In order to enable the system to be close to the inferential thinking of clinical experts, we classified and constructed knowledge of other epilepsy-related knowledge, including mental-psycho functions, brain image findings, epilepsy surgery methods, etc. We used the Ontology Web Language with Description Logic (OWL-DL) and Semantic Web Rule Language (SWRL) to design rules for expressing the relationship between these ontologies.

Afterward, the clinical data of 15 representative cases were used to test the system

Results: We designed an interface for the physician to enter the various characteristics of the patients. Subsequently, the clinical data of 15 representative cases were applied to the AI system. Through SWRL and reasoning engine Drool's execution, 11 cases correctly deduced possible Epileptogenic zone (accurate rate 73.3%). However, this may be limited to the patient's own description and medical records, but this accuracy rate is equal to the accuracy of epileptogenic zone judgment by general epilepsy experts through semiology. However, 13 cases would be correctly diagnosed (accurate rate 86.7%) if EEG data was added for verification.

Conclusions: We clearly showed that our AI system can add to diagnostic yield. In the future, after a larger sample of case tests, we believe that leveraging this AI system in the first line of clinical diagnostics could speed up the confirmation of the diagnosis and help avoid unnecessary high-costing studies.

榮科計畫

TCVGH-NTCNC1118501

臨床護理人員壓力源建模與分析-以急診部門為例

Occupational stress modeling and analysis for nurses -taking critical-emergency unit for example

陳大仁/國立臺中科技大學
徐菀雲/臺中榮民總醫院
李雅婷、葉月珍、翁愷琪、戴于婷、劉輝煌、林家彰、陳韋志/國立臺中科技大學

護理人員為大部分醫療院所的最前線，常面臨重大突發事件、暴力行為、性命攸關處置、外院轉送病人第一線處理等，其所面對的工作環境多為緊張、雜亂、急迫與不愉快甚至是恐懼的氣氛，導致工作壓力高於其他工作。長時間過大的職場壓力，可能引發醫護人員負面的身心症狀、影響照護品質與病人安危。本研究將探究護理人員壓力之風險因子，瞭解這些因子與執業壓力之間的關聯。基於無線人體區域網路(Wireless Body Area Network, WBAN)，建構急診部護理人員生理資訊蒐集與分析系統。研究方法將透過智慧型手機，蒐集 31 位醫學中心護理人員的生理資訊，經過資料清理、去識別化等處理後，透過統計分析與機器學習演算法，根據多種因子與壓力狀況進行建模，找出影響壓力的重要因子、提供管理部門參考。

關鍵詞：職場壓力, 睡眠品質, 工作班別, 自然資料擷取法, 生理訊號測量, 穿戴式技術, 臨床護理人員

Being at the frontline of most hospitals, nurses face the violence, accident, transfers from other hospitals and treatments. Nursing work in the unit suffers more tension, unsystematic, urgent, unpleasant or even terrified atmosphere, so job stress of the nurses is higher than those in other jobs. Such exposure may result in not only injury to nurses' psychosocial and physical health but also negative impact on the quality of patient care and safety. In this project, we investigated nurses' stress level with respect to workplace factor and figures out the connections between the factors of practice stress and stressors. We first constructed an analysis system for nurses' psychosocial and physical signal based on Wireless Body Area Network (WBAN) system. Acquisition data derived through the smart phones from 31 participants were modeled using statistical analysis and machine learning algorithms after data cleaning and Personal Information De-identification processes. These findings of this research help to find the important factors coping the nurses working in emergency, critical and intensive care units, and it would be helpful for nursing administrators as a reference in planning clinical care standard.

Keywords：occupational stress, sleep quality, work shifts, naturalistic acquisition, physiological measurement, wearable technology, clinical nursing.

TCVGH-NTCNC1118502

人工智慧協助大腸切片診斷

Artificial intelligence-assisted diagnosis in colorectal biopsies

李欣倪/臺中榮總病理檢驗部/主治醫師
盧冠霖/國立臺中科技大學中護健康學院護理科/教授
林文彥/國立臺中科技大學資訊流通學院資訊管理系/助理教授
林正堅/國立臺中科技大學資訊流通學院資訊管理系/院長
吳孟玲/成功大學/碩士生

背景:
大腸切片檢體在日常病理診斷上為常見且重要的檢體，可以發現增生性息肉、偵測癌前病變(腺瘤)和癌症，幫助臨床醫師做後續的處理及治療。大腸切片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。因其相對來說較為單純的形態學變化，因此在本院住院醫師訓練過程，分辨大腸切片檢體的良惡性及分類為首要必須具備的能力；若為低度異常(low-grade dysplasia)，則觀察或切除即可，但若為高度異常(high-grade dysplasia and invasive carcinoma)，則須確認是否切除乾淨以及根據侵犯深度接受後續處理。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。此研究計畫欲用電腦深度學習方式，幫忙大腸腺瘤切片型態辨識，把診斷粗略分為低度異常或高度異常(癌化)。

方法:
本院大腸切片診斷腺瘤合併侵入腺癌檢體 20 個個案，調出玻片去辨識並數位掃描後。把影像輸入深度學習工具(此計畫是使用哈佛醫學院、比爾蓋茲基金會與多倫多大學合作的公開模型)，訓練模型判讀型態。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以及測試判讀其他玻片的正確性。

預期結果:
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大腸切片病理診斷的輔助工具，特別是針對在腺瘤背景底下的侵入性癌，不但提供有效率的方法進行偵測，也可將此類的工具代入日常病理診斷工作中，幫忙病理醫師二度確認診斷正確性。

關鍵詞：大腸切片、人工智慧、深度學習、腺瘤、大腸腺癌

Background:
Colorectal biopsied specimens are commonly encountered in daily practice of pathology. The pathologic diagnosis is pivotal to inform clinical physicians about medical conditions, such as normal, hyperplasia, and precancerous lesions (eg. adenoma) and carcinoma, which prompts following managements. Accurate pathologic diagnosis relies on pattern recognition at low

magnifications and cytomorphologic 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 training machine to aid pattern recognition in colorectal biopsied samples, classifying adenoma into low-grade dysplasia and high-grade dysplasia (including adenocarcinoma in situ and invasive carcinoma) categories.

Method:

Colorectal biopsy samples diagnosed as adenoma are scanned in whole slide images. The images are then uploaded to a deep learning tool that creates a machine learning model. Repeat training and testing out the model to ensure the learning machine can correctly classify new examples.

Result:

The accuracy of classification will be evaluated by measuring the sensitivity and specificity by comparing the results of deep learning tool with the diagnosis made by pathologists. The artificial-assisted learning machine/software may aid in the pathologic diagnosis of colorectal biopsied specimens.

Keywords：colorectal biopsy, artificial intelligence, deep learning, tubular adenoma, colorectal adenocarcinoma.

榮逢計畫

TCVGH-FCU1118201

利用AI卷積神經網路分析異常腸鳴音訊號-以腹腔外科手術後評估診斷為例

Using AI Convolutional Neural Network to Analyze Abnormal Bowel Sound Signals-Taking Evaluation and Diagnosis after Abdominal Surgery as an Example

王坤卿/逢甲大學機械與電腦輔助工程學系/教授
沈靜慧/臺中榮民總醫院麻醉部/部主任
蔡鈺鼎/逢甲大學精密系統設計學士學位學程/學程主任
劉凱文/逢甲大學機械與電腦輔助工程學系/研究生
劉柏儀/逢甲大學機械與電腦輔助工程學系/研究生
胡景翔/逢甲大學機械與電腦輔助工程學系/研究生

腸音的診斷比心肺音更為困難；醫生可利用腸道的聲音來診斷疾病，如腸阻塞和麻痺性腸阻塞(paralytic ileus)等疾病，依據腸音的性質或缺失加以判別。臨床上大多仰賴醫生使用傳統聽診器來檢測病人的腸胃蠕動聲音，無法客觀評估及長期監測，容易造成主觀誤判的問題。近年來，儘管目前對於腸音偵測技術進步，但我們對進行自動腸音分析的方法缺乏共識，因此尚未有一個客觀腸音系統，可以提供臨床診斷重要的資訊。

對腸道產生的聲音進行科學分析自 20 世紀初以來，Cannon 已經報導了對腸道產生的聲音的科學分析。然而，對胃腸道產生的聲音的觀察和記錄早在幾個世紀前就已經進行了 Hooke 提出，通過傾聽身體內部零件發出的聲音，有可能發現它們的工作原理。Cannon 描述了腸道中可能由腸道蠕動產生的有節奏的聲音，以及在腸道內強度和位置不同的連續隨機聲音，強度會依據和在腸道內的位置具有不同的連續隨機聲音。據了解，腹部產生的許多聲音是由腸道在消化過程中推動液體和氣體通過腸道而引起的，以及物質通過連接腸道不同部分的閥門時產生的聲音。

本研究以 AI 卷積類神經網路(Convolutional Neural Network, CNN)為基礎的腸音分類演算法，並針對各種訊號的特性與其頻譜分析、時頻分析後的結果，進一步地選擇可匹配的時頻分析結果作為訓練資料。透過 CNN 進行模型建立，並依不同的訊號處理方法所製成的訓練集而優化調整 CNN 架構的詳細參數，比較出 Conv1D、Conv2D(VGG-16)、Conv2D(ResNet50V2)三種網路架構辨識率，提供了對異常腸鳴音訊號分析的初步結果。未來預期使電腦藉由腸音判斷病徵類型，自動歸納、推論可能的病因與治療方案，最後架設雲端運算平台，達到行動監控的功能。

關鍵詞：深度學習、卷積式神經網路、腸鳴音

Diagnosis of bowel sounds is more difficult than heart and lung sounds; doctors can use intestinal sounds to diagnose diseases, such as intestinal obstruction and paralytic ileus, based on the nature or absence of bowel sounds. Most of the clinics rely on doctors to use traditional

stethoscopes to detect the patient's gastrointestinal motility sounds, which cannot be objectively evaluated and long-term monitored, and may easily lead to subjective misjudgment. In recent years, despite the current advances in bowel sound detection technology, we lack a consensus on methods for automatic bowel sound analysis. Therefore, there is no objective bowel sound system that can provide important information for clinical diagnosis.

Scientific Analysis of Sounds Produced by the Gut Since the beginning of the 20th century, Cannon has reported scientific analyzes of sounds produced by the gut. However, observations and recordings of the sounds produced by the gastrointestinal tract have been made centuries before Hooke proposed that by listening to the sounds made by the internal parts of the body, it might be possible to discover how they work. Cannon described rhythmic sounds in the gut that may be produced by peristaltic bowel movements, as well as continuous random sounds that vary in intensity and position in the gut. Many of the sounds produced in the abdomen are known to be caused by the intestines pushing liquids and gases through the intestines during digestion, as well as sounds produced as matter passes through valves that connect different parts of the intestines.

This study uses the AI convolutional neural network (Convolutional Neural Network, CNN)-based bowel sound classification algorithm, and further selects the matching time The frequency analysis results are used as training data. The model is established through CNN, and the detailed parameters of the CNN architecture are optimized and adjusted according to the training sets made by different signal processing methods. The recognition rates of the three network architectures of Conv1D, Conv2D (VGG-16), and Conv2D (ResNet50V2) are compared. Preliminary results of the analysis of the abnormal bowel sounds signal are presented. In the future, it is expected that the computer will use bowel sounds to determine the type of symptoms, automatically summarize and deduce possible causes and treatment options, and finally set up a cloud computing platform to achieve the function of action monitoring.

Keywords：deep learning, convolutional neural network, bowel sound

TCVGH-FCU1118202

利用靜電紡絲技術製備奈米纖維於5-氟尿嘧啶之藥物釋放

Preparation of Nanofibers by Electrospinning Technology for Drug Delivery of 5-Fluorouracil

張育誠/逢甲大學材料科學與工程學系/特聘教授
周佳滿/台中榮民總醫院外科部/主任
石長青/逢甲大學材料科學與工程學系/研究生
邱台意/逢甲大學材料科學與工程學系/專題生

近年來因為癌症逐漸年輕化，進而導致不同類型的化療藥物廣泛被使用於治療各種的癌症。然而過程中往往要透過靜脈注射或攝取方式來進行藥物的傳遞，此將造成一開始藥物攝取濃度過高而後很快即又被代謝掉，而造成藥物的浪費與身體的負擔。若能製備出具備有延緩化療藥物釋放的機制，將能有助於緩慢將藥物進行釋放後，進而用於治療相關的癌症。本計畫使用簡易的靜電紡絲技術製備具有承載 5-氟尿嘧啶藥物之奈米複合纖維，並探討其藥物釋放之效能。在研究中先針對靜電紡絲製備聚乙烯吡咯烷酮奈米纖維之條件進行深入探討後，再進行探討靜電紡絲聚乙烯吡咯烷酮奈米複合纖維與聚乙烯吡咯烷酮奈米複合纖維添加 5-氟尿嘧啶之條件，最後針對奈米複合纖維於 5-氟尿嘧啶之藥物釋放進行不同基質條件下之影響進行研究。由於奈米複合纖維製程簡易且穩定性高，對於不同領域的實際應用具有重要價值。

Recently, cancers have gradually become younger, and different types of chemotherapeutic drugs have been widely used to treat various cancers. However, intravenous injection or ingestion is often used for drug delivery. This method can cause the drug to be ingested at a high concentration at the beginning and then be metabolized soon afterward, resulting in a waste of drugs and a burden on the body. If it can be prepared with a mechanism that delays the release of chemotherapeutic drugs, it can help release the drugs slowly and then treat related cancers. This project uses simple electrospinning technology to prepare composite nanofibers loaded with 5-fluorouracil and explores its drug release efficiency. In the study, the conditions for electrospinning to prepare polyvinylpyrrolidone nanofibers discuss in-depth, and then the conditions for electrospinning polyvinylpyrrolidone composite nanofibers and polyvinylpyrrolidone composite nanofibers with 5-fluorouracil was discussed. Finally, the effect of composite nanofibers on the drug release of 5-fluorouracil under different matrix conditions is studied. Due to the simple process and high stability of composite nanofiber can provide essential value for practical applications in different fields.

TCVGH-FCU1118203

探討慢性阻塞性肺病、空氣污染與基因對心血管疾病的相關性探討

The association of chronic obstructive pulmonary disease, air pollution, and genetic variants with cardiovascular diseases

周天穎/逢甲大學土地管理學系/教授
程建祥/臺中榮民總醫院呼吸治療科/主治醫師
廖勇柏/中山醫學大學公共衛生學系(所)/教授
辜文元/逢甲大學都市計畫與空間資訊學系/助理教授
徐書儀/中山醫學大學公共衛生學系(所)/研究助理
劉紋秀/中山醫學大學公共衛生學系(所)/研究助理
陳霈芯/中山醫學大學公共衛生學系(所)/研究助理
陸玟諭/中山醫學大學公共衛生學系(所)/研究助理
鍾季涵/中山醫學大學公共衛生學系(所)/研究助理

心血管疾病長期以來位居國人十大死因之排名僅次於癌症。人類的疾病是在遺傳背景和環境因素共同作用下產生的，過去已有多篇研究指出慢性阻塞性肺病、空氣污染與心血管疾病有關，後基因體時代的來臨，也有愈來愈多的研究發現與心血管疾病相關的重要基因。因此，本研究目的為探討慢性阻塞性肺病、空氣污染與基因對心血管疾病的相關性研究。本研究以 2008-2019 年臺灣人體生物資料庫已招募的 88,347 名自願參與者為研究族群。空氣污染資料是取自環保署空氣品質監測資料庫，透過地理資訊系統與遙感探測技術來模擬空氣污染濃度之時空變化。研究結果發現，慢性阻塞性肺病、PM2.5 以及 EDN1 rs5370 基因變異是心血管疾的重要危險因子。對於沒有慢性阻塞性肺病的人來說，EDN1 rs5370 帶有 GT+TT 基因型且居住在 PM2.5 濃度大於 32.37207 μg/m3 的地區，其心血管疾病的風險最高。對已經有慢性阻塞性肺病的人來說，PM2.5 的濃度愈高其心血管疾病的風險也愈高，但 EDN1 rs5370 基因型並不會增加心血管疾病的風險。

關鍵詞：心血管疾病、慢性阻塞性肺病、EDN1 基因、PM2.5、地理資訊系統

Cardiovascular diseases (CVDs) rank second to cancer as the leading cause of death in Taiwan. Most diseases are complex and stem from an interaction between genes and the environment. A growing number of studies demonstrates the association between chronic obstructive pulmonary disease (COPD) and CVDs. There is substantial evidence that long-term exposure to air pollution, especially fine particulate matter (PM2.5) contributes to CVDs. Several single nucleotide polymorphisms (SNPs) in genes are associated with COPD and CVDs. However, there is limited knowledge on the joint effect of COPD, environmental, and genetic factors on CVDs. Therefore, the purpose of this study was to explore the association of COPD, air pollution, and genetic variants (SNPs) with CVDs. The research population in this study consisted of 88,347 voluntary participants recruited from the Taiwan

Biobank from 2008 to 2019. The air pollution data were collected from 73 fixed air quality monitoring stations supervised by EPA of Taiwan. We used Geographic Information Systems and Remote Sensing technology to assess the spatial and temporal variability of air pollutants. The study results indicated that COPD, PM2.5 and EDN1 rs5370 gene variant are important risk factors for CVDs. Among non COPD participants, CVDs risk was greatest among those with EDN1 rs5370-GT+TT genotype who lived in areas with PM2.5 concentration greater than 32.37207 μg/m3. In COPD participants, higher PM2.5 concentrations were associated with increased CVD risk; however, the EDN1 rs5370 genotype was not related to CVD risk.

Keywords：Cardiovascular diseases (CVDs), chronic obstructive pulmonary disease (COPD), EDN1 gene, $PM_{2.5}$, Geographic Information Systems

TCVGH-FCU1118204

透明質酸修飾之靛氰綠-聚乳酸甘醇酸奈米膠囊作為診斷淋巴水腫之螢光探針

Hyaluronic acid capped ICG-PLGA Nanocapsule as Fluorescence Probe in Lymphedema Diagnosis

簡儀欣/逢甲大學材料科學與工程學系/副教授
賴志昇/台中榮民總醫院整形外科/主治醫師
馮金星/台中榮民總醫院整形外科/醫事技術師
黃偉任/逢甲大學材料科學與工程學系/碩士班
管宜君/逢甲大學材料科學與工程學系/大學部
楊舒婷/逢甲大學材料科學與工程學系/大學部
戚庭禎/逢甲大學材料科學與工程學系/大學部

全球有超過 2 億人口面臨輕度或中、重度的肢體淋巴水腫的問題，淋巴管靜脈管吻合手術結合靛氰綠螢光分子 (Indocyanine green, ICG) 淋巴管顯影劑為主要的臨床治療方式。嚴重的肢體淋巴水腫經常伴隨患者的淋巴管嚴重阻塞，導致淋巴液外露於淋巴管外部造成腫脹，在注射 ICG 螢光分子的過程，ICG 螢光分子所產生的影像會在體內呈現散亂的影像，使得醫師無法精確判讀淋巴管，為了精準且快速的辨識功能良好的淋巴管，本年度的研究計畫主要開發透明質酸-聚乙二醇-靛氰綠-聚乳酸-甘醇酸 (HA-PEG-ICG@PLGA NPs) 奈米複合材料作為淋巴管螢光顯影劑，由研究內容說明我們成功地製備聚乳酸-羥基乙酸共聚物奈米球 (poly(lactic-co-glycolic acid) nanoparticles, PLGA NPs)，其奈米球的尺寸大小為 489±209 nm，包裹 ICG 螢光分子的 PLGA NPs (ICG@PLGA NPs) 尺寸大小則為 593±225 nm，將胺基化聚乙二醇 (NH2-PEG-NH2) 修飾於 ICG@PLGA NPs，有助於延長奈米載體在血液循環的半衰期。藉由紫外光-可見光吸收光譜儀與螢光光譜儀量測 ICG@PLGA NPs 與 NH2-PEG-ICG@PLGA NPs，皆保有與 ICG 螢光分子相同的光學特性，其最大吸收峰位於 781 nm 且螢光放光訊號峰位於 810-820 nm 區間，以界達電位分析儀確認 ICG@PLGA NPs 與 NH2-PEG-ICG@PLGA NPs 的表面電荷分別為-50.1±1.56 mV 與 0.3±0.36 mV。將透明質酸 (Hyaluronic acid, HA) 修飾於 NH2-PEG-ICG@PLGA NPs 之表面，進行專一性地標定淋巴管內皮透明質酸受體 (LYVE-1) 的細胞實驗。我們預期本次研究計劃所合成具有高生物相容性的透明質酸-聚乙二醇-靛氰綠-聚乳酸-甘醇酸 (HA-PEG-ICG@PLGA NPs) 能夠作為專一性標定淋巴管之奈米螢光顯影劑以達到提高診斷淋巴水腫之精準度。

Over 200 million patients faced the Limb Lymphedema with different stages around the world. In general, the lymphovenous anastomosis had been mainly used as a clinical treatment corresponding to combining the indocyanine green (ICG) fluorescence molecule as a contrast agent in the hospital. The patients with Limb Lymphedema in three or four stages represented terrible lymphatic occlusion regarding the ICG molecule were diffused out of the lymphatic

vessels during the ICG injection. In order to precisely and fast identify the well-functionalized lymphatic vessels through ICG fluorescence imaging. In this study, we successfully synthesized multi-functionalized PLGA (poly(lactic-co-glycolic acid)) nanocarrier to capsule ICG molecule into PLGA nanosphere (ICG@PLGA NPs) by using the microemulsion method. The diameter of PLGA NPs and ICG@PLGA NPs were 489±209 nm and 593±225 nm, respectively. Thereafter, the amine-polyethylene glycol (NH2-PEG-NH2) polymer had been conjugated to the surface of ICG@PLGA NPs for increasing the blood circulation time. Accordingly, the ICG@PLGA NPs and NH2-PEG-ICG@PLGA NPs kept the similar optical properties as ICG molecule of absorbance peak at 781 nm and emission peak at 810-820 nm by UV-Vis spectrometer and fluorescence equipment. Besides, the zeta potential of ICG@PLGA NPs and NH2-PEG-ICG@PLGA NPs was individually measured by -50.1±1.56 mV and 0.3±0.36 mV. Finally, the hyaluronic acid (HA) molecule for specific targeting to lymphatic endothelial receptor (LYVE-1) was conjugated to NH2-PEG-ICG@PLGA NPs. The on-going in-vitro study will be done as soon as possible and demonstrate a highly targeting affinity to endothelial cell of blood vessel conjugation. We hope that the biocompatible HA-PEG-ICG@PLGA nanocarrier will acted as a lymphatic vessel fluorescence nanoprobe for targeting and diagnostic in lymphedema.

TCVGH-FCU1118205

人工智慧技術用於未閉導管的血流動力學變化辨識系統

Applying artificial intelligence technology for the hemodynamic identification system of patent catheter

蔡鈺鼎/逢甲大學精密系統設計學士學位學程/副教授兼主任
林明志/兒童醫學中心/主任
王坤卿/逢甲大學機械與電腦輔助工程學系/教授
黃立誠/逢甲大學電聲學程/研究生(實驗內容撰寫)
李宗毅/逢甲大學電聲學程/研究生(圖文內容撰寫)
宋汶翰/逢甲大學電聲學程/研究生(部分內容撰寫)
林珀攸/榮總(數據彙整)
王德明/榮總/醫師(醫學數據分析)
許雅淇/榮總/醫師(醫學數據分析)
徐仲庭/榮總/醫師(醫學數據分析)
林怡瑄/榮總/醫師/(醫學數據分析)

本計畫提出一新型研究，針對超音波量測到的血流動力學影像，利用影像辨識與人工智慧技術發展出一種新穎的智慧心臟動力變化識別系統。該技術可配套超音波影像檢測與定制循環系統中所測量的心臟參數，包括左心室舒張期內徑（LVIDd）、收縮期左心室內徑（LVIDs）、收縮末期後壁厚度（Hes）、左心室射血時間（ET）、每秒 RR 間期 (RR) 和收縮末壓 (Pes)，以及左心室率校正後的平均圓周纖維縮短速度 (mVcfc) 和收縮末期壁應力 (ESWS) 等多個心臟參數。接著，該模型使用時序型膠囊神經網絡（CsNN）技術，可以監測開放導管的血流動力學變化並確認患者的心臟收縮情況。

這種新的 AI 模型可識別超聲圖像中心臟探測波線檢測到的波形變換來計算心臟參數，然後使用 CsNN 模型推理來診斷患者的當前的心臟動態情況。

關鍵字：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

This project proposes novelty research using artificial intelligence technology for the hemodynamic change identification system of the patent catheter. This technology can be used to detect the heart parameters measured in the custom circulatory system. The management includes the left ventricular inner dimension diastole (LVIDd), the internal dimensions of the left ventricle during systole (LVIDs), the thickness of the posterior end-systolic wall (Hes), the ejection time of the left ventricle (ET), the RR interval per second(RR) and the end-systolic pressure (Pes). The left ventricular rate corrected average circumferential fiber shortening speed (mVcfc) and end-systolic wall stress (ESWS) use these multiple equations to calculate cardiac parameters. Using a time-sequential type of capsule neural network (CsNN) technology, the model can monitor the hemodynamic changes of the open catheter and confirm the patient's heart contraction.

This new AI model uses ultrasonic image and AI feature recognition technology to detect

the custom circulatory system which recognizes the waveform transformation detected by heart detective wave lines in the ultrasound image to calculate the heart parameters, and then uses the CsNN model inference to diagnostic the patient's current cardiac dynamic situation.

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

TCVGH-FCU1118206

兒童早期療育評估與機構篩選優化

Early Childhood Treatment Process and Institutional Screening Optimization

蔡耀德/逢甲大學國際經營與貿易學系/副教授
李友淳/台中榮民總醫院復健科/醫師
翁紹仁/東海大學工業工程與經營資訊學系/教授
陳誌皜/東海大學工業工程與經營資訊學系/博士生
莊友廷/東海大學工業工程與經營資訊學系/工程師

政府針對兒童早期療育有一系列完善的方針，在早療機構的協助下，能及早的判斷6 歲以前的嬰幼童是否有發展遲緩的問題，並給予合適的療癒，然而目前有兩大問題，第一，每年給予醫療院所的早療名額是有限的，且目前的預約掛號系統是以打電話或線上為主且各家醫療院所的系統互不相通，家長會為了能夠搶到有限的名額而不斷的來電諮詢，造成醫療人力的吃緊與資源的浪費，第二，由於判斷幼童是否遲緩是紙本作業，也並未有格式化的表單進行有效溝通，同樣的浪費醫療資源。因此本研究設計線上早療預約系統，使家長能在最短的時間完成掛號預約並減少焦慮感，同時減輕醫護人員的負擔。

The government has a series of comprehensive guidelines for early childhood treatment. With the assistance of early treatment institutions, it is possible to determine early whether infants and young children under the age of 6 have developmental delays and provide appropriate treatment. However, there are currently two major problems. First, the number of early treatment quota given to medical institutions is limited every year. The current appointment registration system is mainly based on telephone calls or online and the systems of various medical institutions are not connected to each other. The constant calls for consultations have caused a shortage of medical manpower and a waste of resources. Second, since judging whether a child is developmental delay is a paper-based operation, and there is no formatted form for effective communication. It also wastes medical resources. Therefore, this study designed an online early treatment appointment system, so that parents can complete the registration appointment in the shortest time and reduce anxiety, while reducing the burden on medical staff.

榮葉計畫

TCVGH-DYU1118301

探討北蟲草應用於抗過敏性皮膚炎之分子機轉

Investigation mechanisms of anti-inflammatory effects of Cordyceps militaris CMZ extract on atopic dermatitis model

吳建一/大葉大學藥用植物與食品保健學系/教授
李美芳/臺中榮總研究部/副研究員
朱裕文/臺中榮總藥學部調劑科/主任

美國蟑螂會誘發呼吸道過敏病，在台灣是僅次於塵蟎之室內過敏原。多年來中榮過敏免疫實驗室致力於蟑螂過敏原分子免疫機轉的探討，以及其臨床診斷指標性過敏原的建立與開發治療的新策略。而以北蟲草作為傳統中草藥使用已經歷數世紀之久。第一年計畫初步成果證實 *Cordyceps militaris* CMZ 酒精萃取物能抑制人類角質細胞株 HaCaT 表現出 IL-8、GM-CSF 與 CCL-20，具有開發為治療過敏疾病的替代之潛力，但是抗發炎機轉還未被探討。因此本計畫擬探討利用已建立之美蟑過敏原誘發之 Raw264.7 巨噬細胞平台評估 *C. militaris* CMZ 酒精萃取物抗過敏發炎之分子機轉。本研究使用不同濃度美國蟑螂敏原刺激 Raw264.7 細胞株建立體外細胞發炎平台。另外，為了解 *C. militaris* CMZ. 萃取物之抗發炎能力，Raw264.7 細胞將先前處理萃取物 30 分鐘，再以蟑螂過敏原培養 1-24 小時。一氧化氮(NO)之生成將使用 Griess reagent 分析；細胞發炎相關之細胞激素 TNF-α、 IL-1β、IL-6 與 TSLP 等 mRNA 表現量則使用 real-time PCR 進行分析。此外，一氧化氮生成酶(iNOS)、環氧合酶(COX-2) 與 mitogen-activated protein kinases (MAPKs) 磷酸化路徑與 caspase-1 之表現將使用西方墨點法分析。本研究證實蟲生真菌 *C. militaris* CMZ 酒萃物具有抗發炎功效，具有開發為治療過敏疾病的替代藥物潛力。

關鍵字：異位性皮膚炎、蛹蟲草、美國蟑螂過敏原、細胞激素和趨化因子

The American cockroach is the second leading source of inhalant allergen causing allergic airway disease in Taiwan. Previously, we have been working on molecular and immunologic characterization of cockroach allergens in order to design better diagnostic and therapeutic strategies for cockroach allergy. Cordyceps -related species has been used in well-known traditional Chinese medicine for centuries. First year data indicated the ethanolic *Cordyceps militaris* CMZ extracts could decrease of mRNA in IL-8, GM-CSF, and CCL-20 in HaCaT cell model. However, molecular mechanisms of anti-inflammatory underlying its use have not been completely elucidated. This study will aim to examine the molecular mechanisms of anti-inflammatory effect of *C. militaris* CMZ in cockroach allergen-treated RAW 264.7 macrophages. Firstly, RAW264.7 cells will be stimulated with different doses of cockroach allergens to establish the in vitro cell inflammation model. To investigate the anti-inflammation effects of the extracts, RAW 264.7 cells will be treated with the extracts for 30 minutes prior to stimulate with cockroach allergens for 1-24 hours. Nitric oxide (NO) production will be measured using Griess reagent. The mRNA expression levels of

inflammatory cytokines, TNF-α, IL-1β, IL-6 and TSLP will be determined using real-time PCR. Western blotting will be used to determine the protein expression of inducible nitric oxide synthase (iNOS), cyclooxygenase (COX-2), the phosphorylation of mitogen-activated protein kinases (MAPKs) and caspase-1. In the study, we expect screening potential metabolites from the entomogenous fungus *C. militaris* CMZ to find new anti-inflammatory alternative medicine for allergic diseases.

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

TCVGH-DYU1118302

以基因轉殖斑馬魚研究內酰胺酶基因(blaOXA)作用機制分析平台之建立

The establishment of transgenic zebrafish platform on the analyses of functional mechanism of lactamase gene (blaOXA)

黃尉東/大葉大學生物醫學系/副教授兼系主任
曾建豪/台中榮民總醫院感染科/主治醫師
楊明泓/大葉大學生物醫學系/大學部學生
蔡雨潔/大葉大學生物醫學系/大學部學生
程媵雅/大葉大學物醫學系/大學部學生

蒼白桿菌屬（Ochrobactrum spp.）已為知對生物體之免疫缺失及活性影響之病原體，且其過去十年因 OXA 型之內酰胺酶（OXA-type-lactamases）之形成而對內酰胺（beta lactam）抗藥性增加。經對 Ochrobactrum pseudogrignonense 序列分析顯示其染色體上之內酰胺酶序列為其抗多種內酰胺之主要因素。斑馬魚(zebrafish, Danio rerio）因其高生產量、易於飼養及迅速之發育過程及較晚成熟之免疫系統等時間、經費、生理與人力優勢條件，使其成為一小鼠外常被運用以研究人類疾病之發生及治療之試驗模式動物。早期斑馬魚之研究多集中於胚胎發育機制、基因調控及環境毒物對其發育之影響，現已擴展應用於人類疾病、藥物篩選與癌症方面之研究。基因轉殖斑馬魚亦被用以研究傳染性疾病與抗菌能力之測試。本研究室已建立斑馬魚基因轉殖試驗之技術平台，本計畫應用此技術，已建構 blaOXA-GFP 基因載體並轉殖入斑馬魚卵，產製穩定表現綠螢光蛋白-內酰胺酶之 blaOXA-GFP 基因轉殖斑馬魚；其注射後 24 至 120 小時之成功率及存活率分別為 90 至 94%及 75 至 96%。此研究方法之建立及結果，除可為相關研究提供參考與合作之空間外，未來可擴展至感染性疾病基因及藥物之篩檢與分析試驗，期對我國未來之醫學有所貢獻。

關鍵字：內酰胺酶、斑馬魚、基因轉殖

Ochrobactrum spp. has been identified as a new pathogen in individuals with immunodeficiency and immunocompetence, and resistance to beta lactam has grown during the past decade, owing in part to the development of OXA-type-lactamases (blaOXA). The genome of *Ochrobactrum pseudogrignonense* has been sequenced and whose chromosomal-encoded-lactamases are likely the main resistance factors to a broad range of lactams. Zebrafish (*Danio rerio*) are disease-resistant, easy breeding and maintaining, and can produce large amounts of transparent eggs. These characteristics make zebrafish other than mice as a world-wide recognized species for vertebrate embryogenesis, organ development, functional genomics and disease model research in the postgenomics era. Recently zebrafish has been recognized as an infectious disease animal model, through transgene technique, different kind of genes have been injected in zebrafish embryos to study

their development and antimicrobial ability. Using this technique established in our laboratory, the blaOXA-GFP expression vector has been constructed and injected into zebrafish embryo and analyzed. The success rates of zebrafish injected with blaOXA:EGFP vector after 24 to 120 hours were from 90 to 94%, and the survival rates of the embryos were from 75 to 96%. The present data can be applied to explore the biological function of the new beta lactamase though establishment of a platform by using *in vivo* zebrafish model for antibiotic research and further application in anti-antibiotic gene function screening in Taiwan.

Keywords: lactamases, zebrafish, transgene

TCVGH-DYU1118303

探討樹豆根酒精萃取物於角質細胞共同培養模式之抗發炎和抗菌活性

Investigation of Anti-allergic inflammation and Anti-bacterial Effects of Ethanolic Extracts from *Cajanus cajan* Roots by in vitro Co-culture Model

朱裕文/臺中榮總藥學部調劑科/主任
宋祖瑩/大葉大學藥用植物與食品保健學系/教授
李美芳/臺中榮總研究部/副研究員

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。

本研究目標是探討樹豆根酒精萃取物是否具有抗發炎和抗菌活性；(1)探討樹豆根酒精萃取物在金黃葡萄球菌-人類單核球細胞株共同培養平台是否對金黃葡萄球菌具有抗菌活性。(2)探討樹豆根酒精萃取物在金黃葡萄球菌-人類單核球細胞株共同培養平台是否具有抑制與發炎反應相關的細胞因子 IL-1β、IL-6、TNF-α、IL-8、CCL-20 和 GM-CSF。

我們的結果發現樹豆根酒精萃取物抑制金黃色葡萄球菌、耐甲氧西林金黃色葡萄球菌生長能力，可以抑制耐甲氧西林金黃色葡萄球菌(MRSA) 誘發 THP-1 細胞產生細胞激素 IL-1β、IL-6、TNF-α。

以我們目前所知，本研究為第一個建構細菌-角質細胞或蟑螂過敏原-角質細胞共同培養平台探討樹豆根酒精萃取物之抗菌活性和抗發炎反應，以及樹豆根酒精萃取物可能的作用機轉。期望透過這些研究結果，我們探討樹豆根酒精萃取物之抗發炎和抗菌活性可作為異位性皮膚炎的新的治療策略。

關鍵詞：異位性皮膚炎和樹豆根酒精萃取物

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 (1) whether ethanolic extracts from *Cajanus cajan* Roots have antimicrobial activities against S. aureus co-culture with THP-1 cell, (2) whether ethanolic extracts from Cajanus cajan Roots influence on the expression of cytokines IL-1β, IL-6, and TNF-α, IL-8, CCL-20 and GM-CSF induced by S. aureus co-culture with THP-1 cell.

Our data indicated ethanolic extracts from *Cajanus cajan* Roots inhibit *S. aureus* and Multiple-resistant *S. aureus*. We also find that Cajanus cajan ethanolic extracts inhibit expression of IL-1β, IL-6 and TNF-α induced by Multiple-resistant Staphylococcus aureus on THP-1 cells.

This is the first study, to our knowledge, to examine antimicrobial activities and

anti-inflammatory effect of ethanolic extracts of Cajanus cajan roots in human keratinocytes co-culture with cockroach allergen and *S. aureus* and to propose a potential mechanism for atopic dermatitis mediated by ethanolic extracts of Cajanus cajan roots. We expect the results, anti-inflammation and anti-bacterial effects of Cajanus cajan roots, which probably will open the way to new therapeutic strategies for atopic dermatitis.

Keywords：Atopic dermatitis, *and Cajanus cajan Roots.*

TCVGH-DYU1118304

探討黑蒜萃取物改善肥胖相關過敏性呼吸道發炎之功效與機制研究

Study on the effect and mechanism of black garlic on improving obesity-related allergic airway inflammation

蔡仁傑/大葉大學藥用植物與食品保健學系/副教授
曾崇育/臺中榮民總醫院骨科部/主任
陳煜昌/大葉大學藥用植物與食品保健學系/專題生
陳瑀翔/大葉大學藥用植物與食品保健學系/專題生
甘絜瑄/大葉大學藥用植物與食品保健學系/專題生

黑蒜(Black garlic)是由生大蒜經高溫以及高濕度環境下經過梅納(Maillard)反應，使其蒜瓣變成黑色，在先前的研究裡指出，大蒜水溶性萃取物及水溶性硫化物 S-allylcysteine (SAC) 具有改善過敏性氣喘呼吸道發炎功效，推測出黑蒜可能具有改 善過敏性氣喘之功效， 因此，黑蒜具有深入研究的意義。該研究的目的是用氣喘之 動物模型，以研究黑蒜萃取物對塵蟎過敏性氣喘之影響。C57BL / 6 小鼠利用 *Dermatophagoides pteronyssinus* (Der p) 誘導氣喘。犧牲後，我們將測量血清中之 IgE、IgG1 和 IgG2a 以及支氣管肺泡液（BALF）中 IL-4 與 IL-10 之水準。Serum 測量結果表明，黑蒜有明顯降低了 Th2 中 IgE 與 IgG1 之水準，並提高了 Th1 中 IgG2a 之水準；BALF 方面，黑蒜增加了 Th1 中 IL-12 之產量， 且降低了 Th2 中 IL-4 與 IL-5 之產量，最後更增加了 IL-10 之產量，這些結果表明，黑蒜對過敏性 氣喘是具有保護作用的。

Black garlic (Black garlic) is made of raw garlic through the Maillard reaction under high temperature and high humidity so that the garlic cloves turn black. In previous studies, it was pointed out that the water-soluble extract of garlic and the water-soluble sulfide S-Allylcysteine (SAC) improves respiratory inflammation in allergic asthma. It is speculated that black garlic may have the effect of enhancing allergic asthma. Therefore, black garlic has significance for further research. The purpose of this study is to use an animal model of asthma to study the effect of black garlic extract on dust mite allergic asthma. C57BL/6 mice were induced with asthma using *Dermatophagoides pteronyssinus* (Der p). After sacrifice, we will measure IgE, IgG1, and IgG2a in serum and IL-4 and IL-10 in bronchoalveolar fluid (BALF). Serum measurement results showed that black garlic significantly reduced the levels of IgE and IgG1 in Th2, and increased the level of IgG2a in Th1; in terms of BALF, black garlic increased the production of IL-12 in Th1 and decreased IL-1 in Th2. 4 and IL-5 production, and finally increased the production of IL-10, these results show that black garlic has a protective effect on allergic asthma.

榮暨計畫

TCVGH-NCNU1117901

蛻皮激素訊號透過微型核醣核酸 let-7-Complex調節嗅覺感覺神經元影響雄性果蠅同性偏好的求偶行為

Ecdysone-responsive microRNA-let7C regulate olfactory sensory neurons are involved same-sex preferences in *Drosophila* males

傅在峰/國立暨南大學應用化學系暨生物醫學碩士班/教授
林志堅/臺中榮民總醫院精神部/主任
蔡榮宗/國立暨南大學應用化學系/博士後研究員
劉柏廷/國立暨南大學應用化學所/博士生
洪詩純/國立暨南大學應用化學所/碩士生

若在Or67d嗅覺感覺神經元降低蛻皮激素訊號、增強胰島素訊號或青春激素訊號均能明顯誘發雄果蠅同性間的求偶行為，這些內分泌訊息在Or67d嗅覺感覺神經元經由獨立的分子機制運作或透過彼此間的協同合作而抑制雄果蠅間的求偶行為，是此計畫想要釐清的問題。在此計畫中我們初步證實降低蛻皮激素訊號將使得let-7-Complex (let-7-C)微型核糖核酸(microRNA; miRNA)的表現降低，以let-7-C所表現的let-7、mir-100及mir-125為核心，透過蛻皮激素訊號所調節的三種microRNAs可預測數個靶向位於胰島素訊號及青春激素訊號的基因轉錄本，針對let-7 miRNA分別釐清這些預測的靶向基因是否確實受其所調節，初步證實let-7 miRNA參與調節青春激素訊號所活化表現的初始反應基因krüppel homolog 1，因此下調蛻皮激素訊號後因let-7 miRNA表現降低將可能促進該細胞的青春激素訊號增強，同時也發現let-7 miRNA也參與調節胰島素訊號中的chico (為脊椎動物insulin receptor substrates的類似物)，因此下調蛻皮激素訊號後因let-7 miRNA表現降低將可能促進該細胞的胰島素訊號增強。推論三種不同的內分泌訊息在嗅覺感覺神經元中經由蛻皮激素訊號所調節的let-7 miRNA相互協同形成一個緊密連結的內分泌訊息網絡，當蛻皮激素訊號失衡即可能影響該細胞中的胰島素、青春激素訊息，並與果蠅複雜的求偶行為反應有著密切的相關性。

Not only does it suppress ecdysteroid signals, but we also found that direct upregulation of insulin signaling or Juvenile hormone (JH) signaling in Odorant receptor 67d (Or67d) olfactory sensory neurons (OSNs) could induce male to male courtship behavior. In this study, we evidenced an ecdysteroid-responsive let-7-complex (let-7-C) miRNAs involve the male-male courtship regulation in Or67d OSNs. Moreover, ecdysone-responsive *let-7* microRNA might regulate *kruppel homolog 1* (*kr-h1*) that an early response gene of JH signaling. Further, preliminary data shows that *let-7* microRNA also targetd *chico* (a homolog of vertebrate insulin receptor substrates) that modulates insulin/insulin-like growth factor signaling (IIS) pathway. Therefore, downregulation of ecdysone signal may promote the enhancement of Kr-h1-dependent JH signaling and IIS in Or67d OSNs. This is a complex

effect involving multiple molecular interactions, wherein imbalances in intricate endocrine networks affect specific nerve cells to ultimately result in unconventional behavioral responses.

TCVGH-NCNU1117902

利用脈衝雷射的光分解作用下在多孔矽表面生長金/二氧化鈦奈米材料於光誘導表面增強拉曼光譜學應用

Pulsed laser photolysis to fabricate Au/TiO2 nanocomposites on porous silicon substrate applied in photo-induced enhanced Raman spectroscopy

蕭桂森/國立暨南國際大學應用材料及光電工程系/教授
周佳滿/台中榮總小兒外科/主任
黃勝揚/台中榮總小兒外科/醫師
朱智謙/中山醫學大學醫學應用化學系/教授
王秉彥/台灣彰化基督教醫院外科部/主任兼主治醫師
廖素鈺/國立暨南國際大學電機工程學系/博士班學生
高唯甯、李宜真、龔郁涵、魏沛晴、謝佑軒/國立暨南國際大學應用材料及光電工程系/學士班學生

表面增強拉曼散射(Surface-enahnced Raman scattering, SERS)光譜，由於其檢測技術 具備有高靈敏性，因此可以應用於分析及成像等相關用途。光誘導表面增強拉曼光 譜學(Photo-induced enhanced Raman spectroscopy, PIERS)是一種類似 SERS 技術，但 是透過 SERS 基板修飾二氧化鈦 (TiO2)，再藉由預先照 UV 光產生氧空缺，可增加 SERS 基板的金原子表面電荷與待測物電子轉移效率，進而放大拉曼訊號。本計畫目的是將四氯金酸(HAuCl4)與市售的 TiO2 奈米粒子在加入過氧化氫的混和溶液中 利用脈衝雷射的高能量，在多孔矽基板上生長 Au/TiO2 奈米複合材料並用於 PIERS 研究。未來嘗試將此 PIERS 用於偵測生物分子或用於臨床醫學等相關研究。

Surface-enhanced Raman scattering (SERS), due to its high sensitivity in detection, can be applied to analysis and imaging and other bio-related applications. Photo-induced enhanced Raman spectroscopy (PIERS) is a technology similar to SERS, but the SERS substrate is modified with titanium dioxide (TiO2). The oxygen vacancies from TiO2 generated by pre-illuminating UV light, can increase the sensitivity of SERS due to the charge transfer between gold (Au) atom and analyte. The purpose of this project is to use tetrachloroauric acid (HAuCl4) and commercially available TiO2 nanoparticles in a mixed solution with hydrogen peroxide to grow Au/TiO2 nanocomposites on porous silicon substrates under high energy pulsed laser. Further studies will try to use PIERS technology in the detection of biomolecules or for clinical medicine and other related research.

TCVGH-NCNU1117903

子宮內膜癌MMR缺失之臨床病理特性及腫瘤浸潤性淋巴細胞之預後價值及免疫機轉研究

Improved Progression-Free Survival Associated withTumor-Infiltrating Lymphocytes in High-Grade Endometrial Cancer

呂建興/臺中榮總婦女醫學部/婦科主任兼任副部主任
傅在峰/國立暨南大學應用化學系/教授
范鈞婷/臺中榮總婦女醫學部/住院醫師

腫瘤浸潤淋巴細胞 (TIL) 已成為子宮內膜癌 (EC) 的預後標誌物。然而，TIL 在具有不同組織學分級和分子類型（例如錯配修復 [MMR] 缺陷）的 EC 中的作用尚未明確。 我們回顧性納入了 237 名原發性 EC 患者，這些患者接受了腹腔鏡或開腹全子宮切除術和雙側輸卵管卵巢切除術的標準分期手術進行分析。 一位對研究患者訊息不知情的獨立病理學家根據國際免疫腫瘤學生物標誌物工作坊在 2017 年所訂定的方法檢視病理切片以評估 TIL。評估的目標包括無進展生存期 (PFS) 和 總生存期（OS）。 統計使用了 Kaplan-Meier 方法用來計算及繪製 TIL 所影響的 PFS 和 OS 的曲線，以及相關次族群分析（低級別與高級別，MMR 狀態）。追蹤中位數 1.82 年之後，18 名患者出現疾病進展或死亡。 總體而言，TIL (+) 與 PFS 或 OS 無關。 然而，我們確實觀察到 TIL (+) 與高級別 EC 患者的更好 PFS (p = 0.045) 相關，但與低級別腫瘤患者無關 (p = 0.733)。 在 MMR 良好 (p = 0.347) 或 MMR 缺陷 (p = 0.168) EC 患者中未觀察到 TIL 對 PFS 的影響。 TILs 的存在可以預測在高級別 EC 患者有更好的 PFS。我們的結果表明，TIL 可能是這些患者的潛在預後標誌物。

關鍵詞：子宮內膜癌、腫瘤浸潤淋巴細胞、錯配修復、生存結果

Tumor-infiltrating lymphocytes (TILs) have emerged as a prognostic marker in endometrial cancer (EC). However, the role of TILs in EC with distinct histology grades and molecular types (such as mismatch repair [MMR] deficiency) has not yet been made clear. We retrospectively included 237 patients with primary EC who underwent a standard staging operation of laparoscopic or laparotomy total hysterectomy and bilateral salpingo-oophorectomy for analyses. An independent pathologist who was blind to the study patients' information reviewed the pathologic slides to assess TILs according to the method introduced by the International Immuno-Oncology Biomarkers Working Group in 2017. The outcomes of interest included both progression-free survival (PFS) and overall survival (OS). The Kaplan–Meier method was used to determine the curves of PFS and OS according to TILs, and also in the relevant subgroups (low-grade vs. high-grade, MMR-proficient vs. MMR-deficient). After a median follow-up duration of 1.82 years, 18 patients had experienced either disease progression or death. Overall, TILs (+) were not associated with PFS or OS. We

did observe, however, that TILs (+) were associated with a better PFS ($p = 0.045$) in patients with high-grade EC, but not in those with low-grade tumors ($p = 0.733$). The effect of TILs on PFS was not observed in patients with MMR-proficient ($p = 0.347$) or MMR-deficient ($p = 0.168$) EC. TILs were associated with a better PFS in patients with high-grade EC. Our results suggest that TILs may be a potential prognostic marker in these patients.

Keywords: endometrial cancer; tumor-infiltrating lymphocyte; mismatch repair; survival outcome

榮臺計畫

TCVGH-CTUST1117701

COVID-19疫情對透析患者心理健康之影響

The impact of the COVID-19 pandemic on the mental health of dialysis patients

陳呈旭/臺中榮民總醫院腎臟科/主任
葉德豐/中臺科技大學醫療暨健康產業管理系/副教授
鍾牧圻/臺中榮民總醫院腎臟科/主治醫師
何玉瑛/臺中榮民總醫院洗腎室/護理長
張靜宜/臺中榮民總醫院洗腎室/護理師
蕭菁菁/臺中榮民總醫院洗腎室/護理師
陳丁進/中臺科技大學醫療暨健康產業管理系/碩士研究生
楊宜芳/中臺科技大學醫療暨健康產業管理系/碩士研究生

2020 年起，由於各國 COVID-19 疫情不斷爆發，感染者與重症者不斷增加，許多國家醫療體系面臨嚴重挑戰、甚至崩潰，各國不得以祭出強制隔離、封城的手段，希望透過社交距離、減少接觸減緩病毒傳染的速度。由於末期腎病(end-stage renal disease, ESRD)患者伴隨著多種風險因素，例如老年、免疫系統效率低下、心血管疾病、糖尿病和高血壓等，因而特別容易感染 COVID-19。洗腎室的防疫措施，醫院的管制措施，可能使得透析患者在回診時面臨更多的阻礙；而醫院可能停止或限制部分醫療服務使得患者難以獲得其他照護的需求。透析患者即使在正常情況下也有很多心理問題，因此，COVID-19 疫情對透析患者而言是一個巨大的挑戰，在 COVID-19 疫情下，整個環境的劇變不但可能會對透析患者的治療帶來阻礙，也可能加劇其心理與社會的壓力。本研究擬以本院透析患者為對象，探討 COVID-19 疫情期間透析患者憂鬱、焦慮、壓力與失眠等心理健康問題的現狀以及受到疫情衝擊的程度。

本研究以中部某醫學中心透析患者為研究對象，採自擬結構式問卷進行調查，內容包括患者基本特性、憂鬱焦慮壓力量表、失眠嚴重度指數、新冠肺炎疫情對患者的社會心理衝擊等，再將所得資料以 SPSS25.0 軟體進行描述性統計與推論性統計，包括卡方檢定、獨立樣本 t 檢定、檢定廣義線性模型、多元迴歸等。

根據 DASS-21 的結果，透析患者在憂鬱、焦慮與壓力的罹病率分別為 14.3%、40.4%、41.2%；在控制個人特質後，PD 患者在憂鬱、焦慮與壓力的疫情惡化指數與加權分數均顯著高於 HD 患者。根據 ISI 的結果，透析患者的失眠比率為 54.7%；在控制個人特質後，PD 患者在失眠嚴重度惡化指數與加權分數均顯著高於 HD 患者。在社會心理衝擊方面，僅 HD 患者在憂心疫情構面顯著高於 PD 患者，而憂心自己或親友受感染以及因疫情減少社會活動是透析患者感受最高的項目。無法或沒有工作、家庭經濟受到疫情嚴重影響、另有重要疾病須定期到院就診、有抽菸或飲酒習慣是影響心理健康的危險因子，而能自由活動與疫苗接種第四劑則為保護因子。社會心理衝擊與心理健康之原始分數、意情惡化指數及加權分數均呈現顯著正相關。

COVID-19 疫情對透析患者的心理健康有顯著的影響，特別是 PD 患者，由於 PD 患者每月只固定一次回診，醫護人員除了關心患者腎臟照護問題以外，也應同時關心患者的心理健康議題，並適時給予足夠的心理支持。

關鍵詞：新冠肺炎、透析病人、心理健康

Since 2020, the continuous outbreak of COVID-19 in various countries has resulted in an increase in infectious and severe patients. Many countries' healthcare systems were facing serious attacks or even collapse. Governments in various countries had to implement compulsory isolation and lockdown. Reducing contact through social distancing slowed down the virus transmission. End-stage renal disease (ESRD) patients are accompanied by a variety of risk factors, such as old age, inefficient immune system, cardiovascular disease, diabetes, and hypertension, so they are particularly susceptible to COVID-19. Pandemic control measures in hospitals and dialysis rooms may prevent dialysis patients from seeking treatment; and hospitals may suspend or restrict some services, making it difficult for patients to obtain other care. Dialysis patients usually have many psychological problems, so the COVID-19 pandemic is a huge challenge for dialysis patients. Under the COVID-19 pandemic, dramatic changes in the environment may not only hinder the treatment of dialysis patients but may also increase their psychological and social stress. The goal of this study is to measure the status of depression, anxiety, stress, and insomnia of dialysis patients during the COVID-19 pandemic, as well as the extent to which they have been impacted by the pandemic, and to analyze the impact of these mental health problems on the quality of life. In this study, dialysis patients in our hospital are selected as the research subjects, and a self-administrated structured questionnaire is used for investigation. The content includes the personal characteristics of the patient, the depression, anxiety stress scale(DASS-21), the insomnia severity index(ISI), and the socio-psychological impact of COVID-19 pandemic. The data obtained are used SPSS25.0 software for descriptive statistics and inferential statistics, including independent sample t test, one way ANOVA, generalized linear models, Pearson correlation analysis, and multiple regression, etc.

According to the DASS-21 results, the prevalence of depression, anxiety and stress in dialysis patients was 14.3%, 40.4% and 41.2% respectively. After adjusting for personal characteristics, the pandemic worsening index and weighted scores for depression, anxiety, and stress were significantly higher in PD patients than in HD patients. According to the ISI results, the prevalence of insomnia in dialysis patients was 54.7%. After adjusting for personal characteristics, PD patients had a significantly higher pandemic worsening index and a significantly higher insomnia weighted score than HD patients. In terms of socio-psychological impact, only the HD patient was significantly more worried about the pandemic than her PD patient, but the point felt by the dialysis patient was that the pandemic could infect them or their families and friends, there was concern that social activities would

decrease. Unable to work or unemployed, family economy severely affected by pandemic, other major illnesses requiring regular hospital visits, and smoking and drinking habits were risk factors affecting mental health, while being able to move about freely in and the fourth dose of immunization were protective factors. Socio-psychosocial impact was significantly positively associated with the raw scores, pandemic worsening index, and the weighted scores of mental health.

The COVID-19 pandemic has had a significant impact on the mental health of dialysis patients, especially those with PD. Because PD patients only come to the hospital once a month, healthcare workers need to manage not only the patient's kidney problems, but also the patient's mental health and provide appropriate psychological support.

Keywords: COVID-19, dialysis patients, mental health

TCVGH-CTUST1117702

聚乙二醇-AuNP納米複合材料評價間充質乾細胞的生物相容性和分化能力

Evaluation the Biocompatibility Effect and Differentiation Capacity of Mesenchymal Stem Cell by Polyethylene Glycol-AuNP Nanocomposites

楊孟寅/臺中榮民總醫院神經醫學中心/主任醫師
劉百栓/中臺科技大學醫學影像暨放射科學系/教授
洪慧珊/中國醫藥大學醫學院生物醫學研究所/副教授
楊怡津/臺中榮民總醫院神經醫學中心

聚乙二醇 (PEG) 與不同濃度 (~ 17.4、~ 43.5、~ 174 ppm) 的金奈米粒子 (Au) 結合，以研究體外和體內的生物相容性和生物學特性。首先，通過使用紫外-可見光譜（UV-Vis）、傅里葉變換紅外光譜（FTIR）、原子力顯微鏡（AFM）、掃描電子顯微鏡（SEM），對自由基清除能力和水接觸角進行測量。此外，還通過動態光散射 (DLS) 測量評估了 PEG-Au 奈米複合材料的直徑。結果表明，含 43.5 ppm Au 的 PEG 在間充質乾細胞 (MSC) 和成骨分化和脂肪細胞分化，尤其是神經元分化中顯示出優異的生物相容性和生物學特性。事實上，PEG-Au 43.5 ppm 在 MSC 上誘導更好的細胞粘附、增殖和遷移。SDF-1α/CXCR4 軸的高表達可能與 MMPs 的激活有關，也可能促進了 MSCs 的分化能力。此外，它還可以阻止間充質乾細胞的凋亡，抑制巨噬細胞和血小板的活化，以及活性氧（ROS）的產生。此外，在大鼠模型中測量了 PEG-Au 的抗炎、生物相容性和內皮化能力。在將奈米複合材料皮下植入大鼠 4 週後，PEG-Au 43.5 ppm 能夠通過抑制 CD86 表達（M1 極化）來增強抗免疫反應，同時還減少中性粒細胞浸潤（CD45）。此外，PEG-Au 43.5 ppm 可促進 CD31 表達和抗纖維化能力。最重要的是，PEG-Au 奈米複合材料已被證明可以增強 MSC 向各種細胞的分化，包括脂肪、血管、骨組織，尤其是神經細胞。該研究闡明了 PEG 結合適量的 Au 奈米顆粒可以成為一種潛在的生物材料，可以與 MSCs 合作進行組織再生工程。

A polyethylene glycol (PEG) is combined with gold nanoparticles (Au) at various concentrations (~ 17.4, ~ 43.5, ~ 174 ppm) to study biocompatibility and biological properties in vitro and in vivo. First, by using ultraviolet-visible spectroscopy (UV-Vis), Fourier transform infrared spectroscopy (FTIR), atomic force microscope (AFM), scanning electron microscope (SEM), free radical scavenging ability and water contact angle measurement. In addition, the diameter of the PEG-Au nanocomposite was also evaluated by dynamic light scattering (DLS) measurement. According to the results, PEG containing 43.5 ppm Au showed excellent biocompatibility and biological characteristics in mesenchymal stem cell (MSC) and osteogenic differentiation and adipocyte differentiation, especially neuronal differentiation. In fact, PEG-Au 43.5 ppm induced better cell adhesion, proliferation and migration on MSC. The high expression of SDF-1α/CXCR4 axis may be related to the activation of MMPs, and may also promote the differentiation ability of MSCs. In addition, it can prevent the apoptosis of mesenchymal stem cells and inhibit the activation of macrophages and platelets, as well as the

generation of reactive oxygen species (ROS). In addition, the anti-inflammatory, biocompatibility, and endothelialization capabilities of PEG-Au were measured in a rat model. After the nanocomposite was implanted subcutaneously in rats for 4 weeks, PEG-Au 43.5 ppm was able to enhance the anti-immune response by suppressing CD86 expression (M1 polarization), while also reducing neutrophil infiltration (CD45). In addition, PEG-Au 43.5 ppm promotes CD31 expression and anti-fibrosis ability. Most importantly, PEG-Au nanocomposites have been proven to enhance the differentiation of MSCs into various cells, including fat, blood vessels, bone tissues, and especially nerve cells. This study clarifies that PEG combined with an appropriate amount of Au nanoparticles can become a potential biomaterial that can cooperate with MSCs for tissue regeneration engineering.

TCVGH-CTUST1117703

螯合劑-抗體比於89Zr-DFO*-labeled Anti-PD-L1 Antibody之影響

Effects of Chelator-Antibody Ratio on 89Zr-DFO*-labeled Anti-PD-L1 Antibody

黃蜂運/中臺科技大學醫學影像暨放射科學系/助理教授
蔡世傳/台中榮民總醫院核子醫學科/主任
龔瑞英/台中榮民總醫院核子醫學科/醫事放射師

前言：過去幾年，PD-L1/PD-1 免疫檢查點療法在癌症治療上帶來了巨大的變革與突破。鋯-89 免疫正子斷層可用來作為免疫治療時病人治療前的篩選及治療後的療效評估應用，是當前核子醫學相當迫切需要及潛力發展之造影劑。**方法：**利用隨機耦合方法製備不同螯合劑-抗體比（CAR）之 DFO 抗體複合體；緊接，完成鋯-89 之放射標誌程序及純化。完成製備的鋯-89 免疫正子斷層造影劑將以小鼠大腸結腸癌動物腫瘤模型進行體內實驗評估，包括正子造影、影像半定量分析及生物分佈評估。**結果：**不同螯合劑-抗體比從 1 到 3 之 DFO 抗體複合體順利完成製備及相關特性分析。鋯-89 標誌之免疫正子斷層造影劑其放射化學產率及放射化學純度可分別達 92%及大於 98%。體內研究結果顯示，鋯-89 標誌之免疫正子斷層造影劑能有效累積於腫瘤位置，並於注射後 24 及 48 小時後有最大攝取。**結論：**本研究已成功製備及分析不同 CAR 從 1 至 3 之 DFO 抗體複合體。同時，鋯-89 免疫正子斷層造影劑能有效偵測腫瘤 PD-L1 表現量，有潛力作為免疫檢查點療法之新生物指標。

關鍵詞：鋯-89；免疫正子斷層造影；DFO；免疫檢查點抑制劑

Introduction: The recently emerged PD-L1/PD-1 immune checkpoint blockade therapies have revolutionized cancer treatment over the past few years. Development of ImmunoPET tracer for patient stratification before the therapy and follow-up after the treatment become urgent issue in the field of nuclear medicine. **Methods:** The DFO-B7H1 conjugates with varying chelator-to-antibody ratio were prepared through random conjugation method. Then, the prepared DFO-B7H1 conjugates were radiolabeled with ^{89}Zr and then evaluated in PD-L1 expressed CT-26 mouse model of colorectal cancer. For in vivo study, PET imaging, ROI analysis of PET images and biodistribution experiments were conducted. **Results:** The DFO-B7H1 conjugates with different chelator-to-antibody (CAR) ratio were prepared and presented from 1 to 3. The radiochemical yield and radiochemical purity of ^{89}Zr-DFO-anti-PD-L1-mAb was 92% and larger than 98%, respectively. PET scan of ^{89}Zr-DFO-anti-PD-L1-mAb showed that tracer accumulated in the tumor successfully and reached maximum uptake around 24 h and 48 h postinjection. **Conclusions:** The preparation and characterization of ^{89}Zr-DFO-anti-PD-L1-mAb tracer with CARs of 1 to 3 were established successfully. The tracer displays an excellent ability to image PD-L1 expressed colorectal tumors.

Keywords: ^{89}Zr; ImmunoPET; DFO; immune checkpoint inhibitor

榮興計畫

TCVGH-NCHU1117601

基於深度學習之腎臟病理影像腎絲球分割與型態分類

Deep learning-based glomerulus segmentation and morphology classification in renal pathology images

莊家峰/國立中興大學電機工程學系/特聘教授
莊雅雯/臺中榮民總醫院腎臟科/主治醫師
林冠彣、陳彥伯、陳偉軒/國立中興大學電機工程學系

腎絲球是腎臟病理影像上的重要結構，透過觀察其數量多寡與型態變化，可幫助我們得知腎臟切片的檢體品質是否良好，也能幫助我們判斷患者的疾病嚴重度、急性度與未來可能的預後。本計畫透過深度學習技術，進行腎臟病理影像之腎絲球實例分割與病理型態分類辨識，並透過評估瞭解其分割的實際效能表現與潛在限制。分割的目的在於自動找出腎絲球的輪廓。本計畫提出兩階段式的實例分割，第一階段先偵測腎絲球。第二階段再搭配深度學習網路分類器，進行腎絲球病理型態分類。此外，第二階段亦針對偵測的腎絲球，採用深度學習分割網路進行實例分割。相對於整張影像進行腎絲球語意分割,此法可以減少訓練資料量與提高分割效果。計畫收集了 200 與 400 放大倍率及 H&E 與 PAS 染色的腎臟切片影像來測試所提方法的表現。

Glomerulus is an important microstructure of renal pathology image. We can determine specimen quality in addition to the disease severity, acuity and prognosis of patient via observing the number and morphology of glomeruli. In this project, we aim to propose new deep learning architecture to perform instance segmentation and pathology morphology classification of glomeruli on renal pathology images. The aim of segmentation is to automatically find the contours of glomeruli. This project has proposed a two-stage instance segmentation method. The first stage is responsible for glomerulus detection. The second stage performs morphology classification of detected glomeruli using a deep learning network. This stage also performs instance segmentation on the detected glomeruli. In contrast to performing glomerulus semantic segmentation on a whole renal pathology image, this approach shows the advantages of reducing test time and improving segmentation performance. This project tests segmentation performance of the proposed method by collecting renal pathology images at 200x and 400x magnifications with H&E and PAS stains.

TCVGH-NCHU1117602

在細胞及活體中探討imiquimod誘導黑色素生成的分子機制

The mechanism of imiquimod-induced melanogenesis: the in vitro and in vivo study

謝政哲/中興大學生物醫學研究所/教授
陳怡如/臺中榮民總醫院內科部/主任
李政宜/中興大學生物醫學研究所/博士候選人

黑色素細胞是表皮中的色素生成的細胞，在接受外界刺激後通過黑色素生成(melanogenesis)路徑啟動黑色素(melanin)合成。 黑色素生成代表黑色素成熟的過程，黑色素可以在細胞質中積累或分泌到細胞外空間。 咪喹莫特 (imiquimod, IMQ) 是 FDA 批准的類鐸受體 7 (Toll-like receptor) TLR7 配體，通過激活細胞特異性免疫反應在臨床上用於治療皮膚癌和尖銳濕疣。 高濃度的 IMQ 也直接誘導癌細胞死亡。 在這項研究中，我們將探索 IMQ 誘導的黑色素瘤細胞黑色素生成的機制。 首先，我們證明了低劑量的 IMQ 可以誘導小鼠 B16F10 黑色素瘤細胞中的黑色素生成和分泌。 IMQ 誘導轉錄因子 MITF 的核轉位，上調黑素生成路徑中相關蛋白的表達，增加酪氨酸酶活性，並導致 B16F10 細胞色素沉著。 接下來，我們觀察到 IMQ 誘導的黑色素生成需依賴於細胞內 cAMP 過度積累引發的 PKA 激活。cAMP 積累是由 TLR7 獨立和氧化自由基 ROS 介導的 PDE4B 抑制作用所引起的。 最後，我們利用 TLR7 抑制劑和 TLR7 抑低策略證明了 TLR7 在 IMQ 誘導的黑色素生成中也起著關鍵作用。我們提供的證據表明,低劑量的 IMQ 可以通過 B16F10 黑色素瘤細胞中的 TLR7 依賴性和非依賴性途徑觸發黑色素生成。

Melanocytes are pigmentary generated cells in epidermies and initiate the melanin synthesis through melanogenesis upon receiving the external stimulation. Melanogenesis represents the process of melanin maturation, and the melanin can be accumulated in cytosol or secret to extracellular space. Imiquimod (IMQ) is a FDA-approved TLR7 ligand and uses for treatment of skin cancers and genital warts in clinical through activation of cell-specific immune response. High concentration of IMQ also directly induces cancer cell death. In this study, we will explore the mechanism of melanogenesis in IMQ-induced melanogenesis in melanoma cells. First, we demonstrated that the low dosage of IMQ could induce melanogenesis, melanin production and secretion in murine B16F10 melanoma cells. IMQ induces nuclear translocation of transcription factor MITF, upregulates the expression of melanogenesis-related proteins, increases tyrosinase activity, and leads to pigmentation in B16F10 cells. Next, we observed that IMQ-induced melanogenesis depends on PKA activation which triggered by excessive intracellular cAMP accumulation. The cAMP accumulation is contributed by TLR7-independent and ROS-mediated PDE4B inhibition. Finally, we demonstrated that the TLR7 also plays a critical role in IMQ-induced melanogenesis by using TLR7 inhibitor and TLR7 knockdown strategy. Taken together, we provide the evidence that

low dosage of IMQ can trigger melanogenesis through both TLR7-dependent and -independent pathways in B16F10 melanoma cells.

TCVGH-NCHU1117603

甘胺酸N-甲基轉移基因表達與抗葉酸免疫調節藥物甲氨蝶呤交互影響胞內代謝之動態平衡之研究

Investigation of glycine N-methyltransferase expression on folate mediated one carbon metabolic kinetics in antifolate disease modifying antirheumatic drug methotrexate

蔣恩沛/中興大學食生系/終生特聘教授
陳一銘/中榮免疫風濕科/醫師
蘇雅麗/中興大學食生系/博士後研究員

甘胺酸 N-甲基轉移酶 (glycine N-methyltransferase) 是肝臟中重要的甲基轉移酵素，也是重要的葉酸結合蛋白。人類甘胺酸 N-甲基轉移酶基因突變、低表達或缺失易提升肝臟疾病風險，包括肝纖維化及非酒精性脂肪肝、甚至肝癌。臨床上甲氨蝶呤是風濕性關節炎使用的第一線疾病修飾抗風濕病藥物。然而甲氨蝶呤不僅抑制目標細胞增殖，也可能導致代謝紊亂。我們先前研究發現在甘胺酸 N-甲基轉移酶缺失的細胞中恢復其表達會有效提升細胞內葉酸含量、協助提高葉酸介導之同半胱胺酸再甲基化反應，同時還對細胞甲基平衡具關鍵影響。然而，在甘胺酸 N-甲基轉移酶基因表達缺失的情況下若長期接受低劑量免疫調節甲氨蝶呤治療會如何交互影響細胞內不同代謝路徑則尚未被透徹研究，尤其是甘胺酸 N-甲基轉移酶表達與此抗葉酸藥物在治療中如何調控各項葉酸介導的單碳代謝分流及單碳單元之分配仍待闡明。本研究之目的在於探討甘胺酸 N-甲基轉移酶與低劑量甲氨蝶呤如何交互調節不同的葉酸介導反應以及其中之代謝動態平衡。本研究結合有/無表達甘胺酸 N-甲基轉移酶之細胞模式、穩定同位素追蹤技術、及氣相質譜代謝流追蹤平台，深入研究甘胺酸 N-甲基轉移酶表達與甲氨蝶呤如何交互影響甘胺酸裂解系統及粒線體單碳代謝反應。結果發現，表達 N-甲基轉移酶會顯著降低透過粒線體中甘胺酸裂解系統衍生之單碳單元-甲酸合成脫氧胸嘧啶及絲胺酸，而甘胺酸 N-甲基轉移酶缺失會改變甲氨蝶呤對甘胺酸利用及粒腺體甘胺酸裂解系統單碳單元生成與利用。甲氨蝶呤在細胞中會造成代謝路徑混亂,而在缺失甘胺酸 N-甲基轉移酶之細胞中恢復此酶表達會則會逆轉部分甲氨蝶呤特定代謝路徑的抑制。我們的研究模式可以作為研究甘胺酸 N-甲基轉移酶與藥物如何交互影響代謝平衡之重要模式，並提供臨床類風濕關節炎用藥重要資訊。

關鍵字: 甲氨蝶呤；甘胺酸 N-甲基轉移酶；甲酸；甘胺酸裂解系統；檸檬酸循環；代謝路徑追蹤

Background. GNMT expression is essential for intracellular folate status and methyl group homeostasis. Mutations in glycine N-methyltransferase (*GNMT*) gene and defected GNMT enzyme have been linked to advanced fibrosis and non-alcoholic fatty liver disease (NAFLD). Methotrexate (MTX) is commonly prescribed for treating human rheumatic diseases. MTX not only inhibits cell proliferation but also results in metabolic perturbations.

We recently demonstrated that MTX selectively inhibits the partitioning of mitochondria derived formate metabolic fluxes via mitochondrial serine hydroxymethyltransferase and glycine cleavage system (GCS), but promoted the fractional metabolic fluxes from cytosolic serine hydroxymethyltransferase. **Objective** of the present study was to investigate how GNMT may influence folate mediated metabolic kinetics including GCS and mitochondrial one carbon metabolism during low-dose MTX therapy. **Design.** Combining cell models (HepG2 $^{GNMT-}$ and *GNMT*-expressing HepG2 cells $^{GNMT+}$, and stable isotopic tracer studies with gas chromatography/mass spectrometry platforms, we investigated how *GNMT* function affects metabolic pathwys during low-dose MTX therapy. **Results.** GNMT expression significantly decreased the utilization of GCS derived formate for cytosolic deoxythymidylate and serine synthesis, indicating that defected GNMT may modulate MTX effects on glycine utilization via GCS. **Conclusions.** The present study provides new insights on how GNMT function may affect mitochondria derived formate dependent pathways during MTX therapy, which will benefit patients with rheumatic diseases on MTX therapy.

Keywords：methotrexate; glycine N-methyltransferase; formate; glycine cleavage system; metabolic flux analysis

TCVGH-NCHU1117604

以配體蛋白結合分析法探討腫瘤蛋白 ENOX2 做為新穎抗癌藥物之蛋白標靶及其在大腸癌症治療之應用

Elucidation of ENOX2 as a drug target of the novel chloroacetamidine anthrathiophenediones (CADs) by cellular thermal shift assays (CETSA) and its application in colon cancer therapy

闕斌如/國立中興大學生醫所/教授
陳周斌/臺中榮民總醫院外科部/部主任
伊斯堤/國立中興大學生醫所/博士班學生
邱詩涵/國立中興大學生醫所/碩士班學生

本實驗室在先前的研究中發現腫瘤細胞中的 ENOX2 蛋白質，因其氧化 NADH 並轉化成 NAD+的活性，調控依賴 NAD+為必要因子的 SIRT1 去乙醯基酶活性，而透過 SIRT1 的酵素活性改變其下游多種蛋白的乙醯化程度，我們認為 ENOX-NAD+-SIRT1 調控軸因此可影響多元的生物功能，如細胞增生、移動、及死亡，因此在腫瘤細胞的存活能力上扮演非常重要的角色。此外，本實驗室與俄羅斯高斯抗生素研究中心合作多年，以多重藥理學的概念探討新穎化合物的生物影響，而利用 anthrathiophenediones 核心結構所發展的一系列衍生物，被發現可透過凋亡及細胞週期停滯等機制，有效的抑制膀胱癌細胞生長，然而目前尚未找到重要的蛋白標靶，以解釋這類化合物的抗癌活性。因此在本計畫中，我們希望藉由可測量完整細胞和組織中化合物靶標的結合的細胞熱位移測定法，證實 ENOX2 為此抗癌藥物的作用標靶。在細胞熱位移測定結果中發現， ENOX2 與 anthrathiophenediones 系列衍生藥物可直接結合，並透過衍生物與蛋白結合的作用，引發 ENOX2 蛋白降解及抑制 SIRT1 去乙醯基酶活性，進而抑制大腸腫瘤細胞的生長。此計畫中所產生的正面的結果，將可衍生出新的癌症治療策略，如以標的蛋白降解技術設計小分子化合物，增強腫瘤細胞的 ENOX2 蛋白降解，並誘發腫瘤細胞的凋亡; 此技術將可應用在腫瘤抑制及有助於臨床上腫瘤治療、轉譯及精準醫學的研究與發展，在社會及經濟層面下具有重要的意義。

ENOX2 protein is universally expressed in cancer/transformed cells and exhibits many characteristics associated with cancer. We have sufficiently demonstrated that ENOX2 regulates cancer cell proliferation, migration, and apoptosis through SIRT1 (silent mating type information regulation 1) deacetylase, given that ENOX2 oxidizes NADH to generate NAD+ and NAD+ is also a cofactor for SIRT1 activation. Moreover, effective ENOX2 downregulation by anticancer drugs triggers apoptosis and growth inhibition. Most recently, in collaboration with our Russian partners at the Gause Institute of New Antibiotics, we have reported a novel series of chloroacetamidine anthrathiophenediones (CADs) derivatives that can induce apoptosis and cell cycle arrest in bladder cancer cells, however, without specific protein target being identified. In this regard, we speculate that tNOX is the drug target for these derivatives contributing to their cytotoxicity. In this project, we propose to validate that

ENOX2 directly binds to certain derivatives as drug targets by the cellular thermal shift assay (CETSA) and isothermal dose-response fingerprint (ITDRFCETSA) curves. To achieve this purpose, we have proposed three specific aims in this study, including 1) To demonstrate that individual derivative directly engages ENOX2 in colon cancer cells, a cellular thermal shift assay (CETSA) and isothermal dose-response fingerprint (ITDRFCETSA) curves will be conducted and established to demonstrate the direct binding of ENOX2 and individual derivative. 2) To validate that the direct binding between ENOX2 and individual derivatives results in an inhibition of ENOX2 activity and an enhancement in protein degradation in colon cancer cells. 3) To confirm that the direct binding between ENOX2 and individual derivative results in an inhibition of SIRT1 activity and suppression of growth of colon cancer cells. It is our belief that the binding of the CADs to the ENOX2 protein could very possibly result in ENOX2 downregulation and inhibition on the ENOX2-NAD+-SIRT1 axis through the deacetylase activity of SIRT1 on downstream substrates, such as p53 and others, ultimately affect many cellular outcomes. We also propose that CADs-mediated ENOX2 downregulation may assist in the design and synthesis of ENOX2 degradation chimera molecules by tethering the most effective CADs with ligands to E3 ligase for further ENOX2 degradation in vitro could be derived in our next project. The results generated from these studies will be powerful biological and pharmacological agents that can be developed as a new type of therapy for cancer management.

TCVGH-NCHU1117605

評估肌肉注線粒體對神經擠壓傷後的神經和肌肉再生的可能性

Assessment of regeneration in the nerve and muscle by intramuscular infusion of mitochondria in a nerve crush injury

蘇鴻麟/中興大學生命科學系/教授
潘宏川/臺中榮總醫學研究部/科主任

周邊神經損傷通常致神經纖維的退化和神經支配肌肉的去神經支配化。凋亡的去神經細肌肉胞會減少線粒體含量並產生肌肉萎縮。肌肉細胞凋亡是有組織改變細胞特性，包括了形態特徵，質膜的浮泡和核分解和 DNA 斷裂。肌肉去神經化會能導線粒體含量的變化，導致 Bax 升高和 Bcl-2 降低以及 Bax 與 Bcl-2 的比例顯著上升。在我們以前的發表的文獻中，我們發現體外注射線粒體可以增加神經或大腦的功能。因此本研究在評估線粒體的灌注在去神經支配的肌肉，去研究神經和肌肉修復的可能機轉。在這個研究中，利用我們以前已經發表的肌肉去神經的模式來評估肌肉灌注射線粒體的潛力，以評估肌肉萎縮的功能恢復和保護的機轉。

本研究設計如下，包括短期的壓傷神經產生去神經的肌肉來觀察肌肉灌注線粒體的效益以及左坐骨神經壓損傷的模式來研究長期的功能評估。此外，使用雙氧水引導 C2C12 的細胞株產生細胞凋亡來模擬去神經的肌肉，研究線粒體的共同培養所產生保護的可能機轉。

研究的數據顯示，線粒體注射後，可以均勻分佈於去神經支配的肌肉中而線粒體的數量和乙酰膽鹼受體的表現呈正相關。線粒體注射之後，可以減弱因去神經的肌肉所增加的 caspase 3, 8 oxo-dG, Bad 和 Bax。去神經支配肌肉中 Bcl-2 表達的下降可因過線粒體注射而增加。此外，線粒體注射可以增加 desmin 和乙酰膽鹼受體的表達且恢復神經和肌肉的型態。此外在神經學的分析上，我們發現線粒體注射可以增加 CMAP 和 latency 及 SFI 的改善。

總之，線粒體的補充可以成功地預防周邊神經損傷所產生的去神經支配的肌肉萎縮。我們的研究發現，線粒體注入去神經支配的肌肉可以減少肌肉和神經的氧化壓力，並增加神經再生。此模式有可能應用於人類因神經損傷造成肌肉的萎縮。

關鍵字: 肌肉去神經支配，線粒體，細胞凋亡

Peripheral nerve injuries result in muscle denervation with the involved muscle undergoing apoptosis which subsequently reduced mitochondrial contents and caused muscle atrophy. Local injection of mitochondria had been suggested a useful tool to restore the injured nerve or brain function. However, the supplement of mitochondria in the denervated muscle after nerve injury had not been investigated. This study conducted the intramuscular infusion of mitochondria in the denervated muscle induced by a nerve crush to assess the possible mechanism involved in nerve regeneration.

In this proposal, we utilize our previous muscle denervation mode to assess the potential of intramuscular infusion of mitochondria to investigate the function recovery and protection of muscle atrophy.

The study was designed as below including the short term assessment of intramuscular infusion of mitochondria (195 g) upon denervated muscle 7 days after nerve injury and the long term assessment of neurological outcome conducted by left sciatic nerve crush injury. We also mimic the denervated muscle apoptosis by using the C2C12 myotube cells line induced by H2O2 and to assess the effect of mitochondria in the prevention of myotube apoptosis.

The results showed that intramuscular infusion of mitochondria was homogenously distributed to the denervated muscle and the amount of mitochondria paralleled the expression of acetylcholine receptor. The increased caspase 3, 8 oxo-dG, Bad, and Bax were attenuated by mitochondria infusion. The down-regulation of Bcl-2 expression in denervated muscle was reciprocally augmented by the mitochondria injection. In addition, the decreased expressions of desmin and acetylcholine receptor were counteracted by mitochondria injection. We found that mitochondria infusion could augment the improvement of SFI and electrophysiology data of CMAP and conduction latency.

In conclusion, the supplement of mitochondria can successfully prevent the peripheral nerve injury and denervated muscle atrophy. Our studies had the potential that mitochondria injection into the denervated muscle can reduce the oxidative stress of muscle and nerve and augment the nerve regeneration.

Keywords：muscle denervation, mitochondria, apoptosis

TCVGH-NCHU1117606

研究丹參酚酸B鎂鹽對肥胖性肌少症之保健功效及其可能分子機轉

Studies on the preventive effects of Magnesium lithospermate B on obese sarcopenic and their putative molecular mechanisms

陳文英/國立中興大學獸醫學系所/教授
吳志成/臺中榮民總醫麻醉部疼痛科/科主任
黃瑋琪/國立中興大學獸醫學系所/博士生
賴宛平/國立中興大學獸醫學系所/碩士生

丹參酚酸 B 鎂鹽（Magnesium Lithospermate B, MLB）是丹參的主要活性成分，我們之前的研究證實 MLB 對肥胖相關代謝異常具有改善作用。 本研究主要探討 MLB 在高脂肪飲食 (HFD) 誘導的肥胖小鼠中對抗肌肉萎縮的潛力。 高脂肪飲食除引發代謝異常外，也促使小鼠的骨骼肌重量和肌肉纖維出現流失的現象，肌肉專一性的 ubiquitin E3 ligases, 如肌肉萎縮 F-box (MAFbx) 和肌肉環指蛋白 1 (MuRF- 1)的表現量增加。 MLB 補充有效減緩了高脂飲食導致的這些健康問題。 同時高脂肪飲食亦導致小鼠血液中腫瘤壞死因子-α (TNF-α) 和白細胞介素-6 (IL-6)的含量增加；骨骼肌中 TNF 受體 (TNFRI)、p65 磷酸化和 FoxO1 的表現增加；以及降低骨骼肌中 PI3K 的表現 和 Akt 的磷酸化。這研究證實 MLB 可能通過抑制 MAFbx/MuRF-1 介導的肌肉降解來預防肥胖所引發相關的骨骼肌萎縮。 PI3K-Akt-FoxO1 通路的激活和 TNF-α/TNFRI/NF-κB 通路的抑制被認為是 MLB 的有益作用。

關鍵字: 丹參酚酸B鎂鹽、肌肉萎縮、肥胖、胰島素阻抗、發炎

Magnesium lithospermate B (MLB) is a primary hydrophilic component of Danshen, the dried root of Salvia miltiorrhiza used in traditional medicine, and its beneficial effects on obesity-associated metabolic abnormalities were reported in our previous study. The present study investigated the anti-muscle atrophy potential of MLB in mice with high-fat diet (HFD)-induced obesity. In addition to metabolic abnormalities, the HFD mice had a net loss of skeletal muscle weight and muscle fibers and high levels of muscle-specific ubiquitin E3 ligases, namely the muscle atrophy F-box (MAFbx) and muscle RING finger protein 1 (MuRF-1). MLB supplementa-tion alleviated those health concerns. Parallel changes were revealed in high circulating tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), skeletal TNF receptor I (TNFRI), nuclear fac-tor-kappa light chain enhancer of activated B cells (NF-κB), p65 phosphorylation, and Forkhead box protein O1 (FoxO1) as well as low skeletal phosphoinositide 3-kinase (PI3K) and protein ki-nase B (Akt) phosphorylation. The study revealed that MLB prevented obesity-associated skele-tal muscle atrophy, likely through the inhibition of MAFbx/MuRF-1-mediated muscular degra-dation. The activation of the PI3K-Akt-FoxO1 pathway and inhibition of the TNF-α/TNFRI/NF-κB pathway were assumed to be beneficial effects of MLB.

Keywords：magnesium lithospermate B; muscle atrophy; obesity; insulin resistance; inflammation

TCVGH-NCHU1117607

PAX3 在臺灣神經膠質瘤中的複製壓力與抗藥性關係探討

The role of PAX3 involved in drug resistance and replication stress in glioma cells from Taiwanese.

沈炯祺/中榮神經外科/主任
楊文明/興大分子生物所/教授
吳慈華/興大分子生物所/助理
趙孟秦/興大分子生物所/兼任助理
劉維新/興大分子生物所/兼任助理
侯帛邑/興大分子生物所/兼任助理

基因不穩定是導致癌症的主要原因。 過去發現基因不穩定性是由於 DNA 複製過程中 DNA 受阻無法複製，造成複製叉停滯和複製壓力。DNA 雙股斷裂後，細胞會通過 ATR 磷酸化誘導複製壓力反應，消除 DNA 複製過程中的障礙，使 DNA 複製順利進行。如果不解決複製壓力，就會發生 DNA 損傷並隨後導致基因組不穩定。因此許多引起強烈複製壓力的基因毒性藥物目前被應用於癌症治療。然而， 基因不穩定的癌細胞會進化為耐藥性以生存並導致死亡率。癌細胞的抗藥機制尚不清楚。過去的研究發現，轉錄因子 PAX3 在許多癌細胞中高表達，包括膠質母細胞瘤，在降低 PAX3 表達並且用抗癌藥物治療後易導致膠質母細胞瘤細胞死亡。先前我們已經證明 PAX3 定位於複製叉，PAX3 減少了抗癌藥物引起的複制壓力，保持基因組穩定，基於這些發現，我們推測 PAX3 可能使神經膠質瘤細胞中的 DNA 保持穩定。此外 PAX3 具有在接受化學療法或放射療法時保持神經膠質瘤細胞存活的功能。我們與台中榮民總醫院 (TCVGH) 合作，評估 PAX3 是否可以通過膠質母細胞瘤細胞中的基因毒性試劑抑制複製壓力和基因組不穩定性。我們通過測定微核證實膠質母細胞瘤細胞 U87-MG 含有更高的基因組不穩定性， 通過增加 PAX3 的表達來抑制。PAX3 的過表達抑制了羥基脲 (HU) 誘導的 U87- MG 和 HEK293 細胞中的γ-H2AX 和 RPA foci，表明 PAX3 可以抑制化療藥物（如 HU）誘導的基因毒性。此外，通過 BLM 和 gamma-tubulin 測定，PAX3 的過表達抑制了 HU 誘導的基因組不穩定性，進一步表明 PAX3 是維持神經膠質瘤基因組穩定性的關鍵。最後，PAX3 的過表達增加了 HU 處理下的細胞存活率， 進一步支持 PAX3 通過解決複製壓力維持基因組穩定性，從而防止神經膠質瘤細胞免受基因毒性誘導的細胞死亡。本研究發現 PAX3 是神經膠質瘤細胞化療耐藥的關鍵因素。我們的結果將幫助研究人員為神經膠質瘤患者開發出更好且急需的療法。目前這一方面的成果已和其他相關的結果彙整為一篇文稿，在準備投稿中。

Genetic instability is the main cause of cancer. In the past, it was found that genetic instability was due to DNA being hindered and unable to replicate during DNA replication, causing replication fork stalling and replication stress. Upon DNA double- strand breaks, the cell will induce a replication stress response through ATR phosphorylation to eliminate

obstacles during DNA replication and to make DNA replication proceed smoothly. If replication stress is not resolved, DNA damage will occur and subsequently cause genomic instability. Based on this, many genotoxic drugs, causing strong replication stress, are currently applied to cancer therapy. However, cancer cells with genome instability evolve to drug resistance to survive and leading to a high mortality rate. The mechanism of drug resistance of cancer cells remains unclear. Past studies have found that transcription factor PAX3 is highly expressed in many cancer cells, including glioblastoma. Glioblastoma cells die after PAX3 expression is knocked down and the glioblastoma cells are treated with cancer drugs. Previously, we have shown that PAX3 localizes to the replication fork, and PAX3 reduces replication stress caused by anti-cancer drugs, keeping the genome stable. Based on these findings, we speculate that PAX3 may keep the DNA stable in glioma cells. Furthermore, PAX3 possesses the function of keeping glioma cells alive when undergoing chemotherapy or radiation therapy. In collaboration with Taichung Veterans General Hospital (TCVGH), we evaluate if PAX3 can suppress replication stress and genomic instability by genotoxic reagents in glioblastoma cells. Here, we report that glioblastoma cell U87- MG contains higher genomic instability through micronucleus assays, which is suppressed by increasing the expression of PAX3. Overexpression of PAX3 suppresses Hydroxyurea (HU)-induced gamma-H2AX and RPA foci in both U87-MG and HEK293 cells, demonstrating that PAX3 can suppress the genotoxicity induced by a chemotherapic drug, like HU. Moreover, overexpression of PAX3 suppresses HU- induced genomic instability by BLM and gamma-tubulin assays, further suggesting that PAX3 is the key to maintaining genomic stability in glioma. Finally, overexpression of PAX3 increases the cell survival rate under HU treatment, further supporting that PAX3 maintains genomic stability through resolving replication stress, thus keeping glioma cells from genotoxic-induced cell death. This study finds PAX3 is the key factor for chemoresistance in glioma cells. Our results will help researchers develop better and desperately needed therapies for glioma patients. One manuscript is under prepared with some of the results from this report.

TCVGH-NCHU1117608

探討家禽里奧病毒調控癌細胞株之細胞激素及immune checkpoint 及 Toll-like receptors

Exploring avian reovirus regulation of cytokines and immune-checkpoint and Toll-like receptors in cancer cell lines

劉宏仁/國立中興大學分子生物學研究所/終身特聘教授兼執行長
廖采苓/台中榮民總醫院醫學研究部/研究員
吳怡瑩/中興大學博士後/研究員
黃韋儒/中興大學博士後/研究員
李俊毅/中興大學博士班/研究生

動物病毒可以避免人類已存在之免疫力，同時具有安全及免疫刺激性。我們以家禽里奧病毒(avian reovirus; ARV) 針對四種癌細胞株（AGS、B16F10、Hela 及 A549）進行了測試。我們發現 ARV 感染癌細胞株後，病毒可於癌細胞株複製及誘導強烈之細胞病變效應 (cytopathic effect; CPE)。特異性免疫是由特異性細胞因子控制。因此，腫瘤免疫微環境(Tumor microenviroment; TME）中特定細胞因子之增加可有助於誘導優化特異性之免疫反應並增強 ARV 之溶瘤效果。為了證明這一假設，在 ARV 感染癌細胞株後，我們測定細胞激素(TH1、TH2 及 TH17)、第 I 型干擾素(type I interferons)、白細胞介素-2 (interleukin-2; IL2)及白細胞介素-6 (interleukin-6; IL6)之表現量。同時也以即時定量 PCR 檢測評估免疫檢查點及 Toll 樣受體(Toll-like receptors; TLRs)之表現量。結果顯示，在感染 ARV 下觀察到 TH1 細胞激素(IFN-γ 及 IL12)於測試之癌細胞株之 mRNA 水平增加。此外，在胃癌細胞株 AGS，在 ARV 感染下可見 DR4 及 DR5 之表現量增加。ARV 可誘導功能性 TNF 相關凋亡誘導配體(TNF-related apoptosis-inducing ligand; TRAIL)在人外周血單核細胞(human peripheral blood mononuclear cell; PBMC)上表現。我們發現 PBMCs 經 ARV 或 UV-ARV 感作 24 小時後，TRAIL 之表現量顯著提升。這些結果顯示免疫反應的方向可以由 ARV 控制，進一步增加 ARV 溶瘤活性。目前已知癌細胞死亡之三種機制是通過導致細胞凋亡、促炎細胞激素及第 I 型干擾素的誘導。在所有癌細胞株中，ARV p17 轉染下可見 IL7 及 IL12 之 mRNA 水平增加。在 AGS 癌細胞株，ARV σC 轉染下可見 DR4 和 DR5 之 mRNA 水平增加。因此，溶瘤 ARV 具有潛力擴展用於治療癌症和其他惡性腫瘤。

關鍵詞：家禽里奧病毒、p17、σC、溶瘤病毒、細胞因子、癌症、免疫檢查點、第 I 型干擾素、白細胞介素

Animal viruses have the possibility to avoid pre-existing immunity in humans, while being safe and immunostimulatory. We used an avian reovirus (ARV) and tested it against a panel of carcinoma cell lines (AGS, B16F10, Hela and A549). We found that ARV σC can replicate in these cancer cell lines and induce strong cytopathic effects (CPE). The direction of

specific immunity is controlled by the specific cytokines. Therefore, the additive of specific cytokines in tumor immune microenvironment (TME) might help to induce an optimized specific immune reaction and enhance the efficacy of ARV oncolytic activity. To prove this hypothesis, grouper TH1, TH2, and TH17 cytokines, type I interferons, interleukin-2 (IL-2) and interleukin-6 (IL-6) were measured. Quantitative real time reverse transcription and polymerase chain reaction (RT-PCR) was also employed to evaluate the effectiveness of immune checkpoints and Toll-like receptors (TLRs). Our results revealed that in groupers, TH1 cytokines (IFN-γ and IL-12) were activated in all cancer cell lines infected with ARV. Furthermore, in AGS, an increased mRNA level of DR4 and DR5 were observed under the treatment of ARV. ARV can induce expression of functional TNF-related apoptosis-inducing ligand (TRAIL) on human peripheral blood mononuclear cell (PBMC). We found that ARV or UV-inactivated ARV upregulates the expression of TRAIL on PBMC populations. These results indicated that the direction of immune response can be controlled by ARV, further increasing oncolytic activity. It was determined that three mechanisms of cancer cell death are through syncytia formation, resulting in apoptosis, pro-inflammatory cytokines, and induction of type I IFNs.We also investigated the effects of p17 and σC proteins of ARV against cancer cell lines. In all cancer cell lines, an increased mRNA level of IL-7 and IL-12 were seen in ARV p17-transfected cancer cell lines. In AGS, an increased mRNA level of DR4 and DR5 were also detected in ARV σC-transfected cancer cell lines. Therefore, ARV can potentially expand the repertoire of oncolytic viruses for treatment of carcinoma and other malignancies.

Keywords: avian reovirus, p17, σC, oncolytic virus, cytokine, cancer, immune checkpoints, type I interferons, interleukin

TCVGH-NCHU1117609

能量代謝訊息路徑對於急性淋巴性白血病之治療潛力機制探討

The mechanism of energy metabolism signaling pathway for the treatment of acute lymphoblastic leukemia

黃芳亮/臺中榮民總醫院兒童醫學中心血液腫瘤科/科主任
李龍緣/國立中興大學生命科學系/副教授
李佳玲/臺中榮民總醫院兒童醫學中心/博士後研究員

T 細胞急性淋巴性白血病是一種未成熟的淋巴細胞腫瘤，其特徵是未成熟的 T 細胞母細胞發生致癌性轉化，能量代謝在癌症的發展中起著重要作用。然而對於 T 細胞急性淋巴性白血病的能量代謝調控的研究仍不多，因此，本研究旨在探討調節能量代謝路徑對 T 細胞急性淋巴性白血病的治療機制。在我們的研究中，發現氯硝柳胺可以有效活化細胞凋亡和細胞自噬，降低戊糖磷酸路徑中轉醛醇酶（TALDO）、轉酮醇酶（TKT）和轉酮醇酶樣 1/2（TKTL1/2）的表現量，抑制 T 細胞急性淋巴性白血病細胞的存活率。然而，氯硝柳胺並不影響急性淋巴性白血病細胞中的氧化壓力。結論，我們的研究指出氯硝柳胺可透通過調節能量代謝信號路徑來抑制 T 細胞急性淋巴性白血病細胞的存活率。

關鍵詞：T 細胞急性淋巴性白血病；能量代謝；轉醛醇酶；轉酮醇酶；細胞自噬

T-cell acute lymphoblastic leukemia (T-ALL) is an immature lymphoid tumor characterized by the oncogenic transformation of immature T-cell progenitors. Energy metabolism plays an important role in the development of cancer. However, there is still little research on the regulation of energy metabolism in T-ALL. Therefore, this study is to explore the therapeutic mechanism of regulating energy metabolism pathways for T-ALL. In our study, we found that niclosamide can effectively activate cell apoptosis and autophagy, reduce the expression of transaldolase (TALDO), transketolase (TKT), and transketolase like 1/2 (TKTL1/2) in the pentose phosphate pathway, and inhibit the viability of T-ALL cells. However, niclosamide did not affect the ROS level in T-ALL cells. In summary, our study indicated that niclosamide could inhibit the cell viability of T-ALL by regulating energy metabolism signaling pathway.

Keywords: T-cell acute lymphoblastic leukemia; energy metabolism; transaldolase; transketolase; autophagy

TCVGH-NCHU1117610

芳基烴受體調節高遷移率族蛋白在內皮細胞和糖尿病動物模型機轉性探討

Aryl hydrocarbon receptor regulates high mobility group box 1 in response to hyperglycemia in endothelial cells and in diabetes animal models

許美鈴/國立中興大學生物醫學研究所/終身特聘教授
王俊興/台中榮總新陳代謝科/主治醫師
邢相媛/國立中興大學生物醫學研究所/研究助理

背景：我們研究了芳基烴受體 (AhR) 對內皮細胞和糖尿病動物模型中高血糖/晚期糖基化終產物 (AGEs) 誘導的高遷移率族蛋白 1 (HMGB1) 的影響。
方法：使用永生化小鼠微血管內皮細胞 (SVEC) 和原代人臍靜脈內皮細胞 (HUVEC) 來研究 AhR 和 HMGB1 在體外對高血糖和 AGEs 治療的反應的表達。 小鼠基因敲除導致的 AhR 缺陷用於研究 AhR 對糖尿病小鼠模型（鏈脲佐菌素 [STZ] 治療或 db/db 小鼠）中 HMGB1 的影響。 招募沒有糖尿病病史的人類受試者，並通過口服葡萄糖耐量試驗 (OGTT) 和糖化血紅蛋白 (HbA1c) 確定他們的葡萄糖調節狀態。 使用 ELISA 試劑盒收集空腹血樣以確定循環 HMGB1 水平。
結果：AhR 和 HMGB1 在 SVEC 和原代 HUVEC 中被誘導以響應高血糖或 AGEs 的治療。 使用電泳遷移率變動分析 (EMSA) 和染色質免疫沉澱 (ChIP) 分析證明了 AhR 蛋白和 HMGB1 基因啟動子之間的相互作用。 此外，這種相互作用被 AhR 拮抗劑消除了。 在糖尿病小鼠模型中，STZ 治療或 db/db 小鼠的主動脈內皮循環 HMGB1 和 HMGB1 表達增加。 在 AhR 基因敲除小鼠中沒有發現 HMGB1 增加。 在人類受試者中，新診斷糖尿病患者的循環 HMGB1 增加。
結論：AhR 調節 HMGB1 以響應內皮細胞和糖尿病動物模型中的高血糖/AGE。

關鍵詞: 晚期糖基化終產物，芳基烴受體，糖尿病，高遷移率組框 1

Background: We investigated the effects of aryl hydrocarbon receptor (AhR) on hyperglycemia/advanced glycation end products (AGEs)-induced high mobility group box 1 (HMGB1) in endothelial cells and in diabetes animal models.
Methods: Immortalized mouse microvascular endothelial cells (SVEC) and primary human umbilical vein endothelial cells (HUVEC) were used to investigate the expression of AhR and HMGB1 in response to hyperglycemia and AGEs treatment *in vitro*. AhR deficiency by genetic knockout in mice was used to study the effects of AhR on HMGB1 in diabetes mouse models (streptozotocin [STZ] treated or *db/db* mice). Human subjects with no history of diabetes were enrolled and their glucose regulation status was determined with oral glucose tolerance test (OGTT) and glycated hemoglobin (HbA1c). Fasting blood samples were collected to determine circulating HMGB1 levels using an ELISA kit.
Results: Both AhR and HMGB1 were induced in SVEC and primary HUVEC in response to

treatment of hyperglycemia or AGEs. An interaction between AhR protein and HMGB1 gene promoter was demonstrated using electrophoretic mobility shift assays (EMSA) and chromatin immunoprecipitation (ChIP) assay. Moreover, the interaction was abolished by AhR antagonist. In diabetes mouse models, there was an increase in circulating HMGB1 and HMGB1 expression in aortic endothelium in STZ-treated or *db/db* mice. No increase in HMGB1 was noted in AhR knockout mice. In human subjects, circulating HMGB1 was increased in subjects with newly diagnosed diabetes.
Conclusions: AhR regulates HMGB1 in response to hyperglycemia/AGE in endothelial cells and in diabetes animal models.

Keywords：advanced glycation end product, aryl hydrocarbon receptor, diabetes, high mobility group box 1

TCVGH-NCHU1117611

新型光驅動藥物與紫杉醇之協同作用：經由基因調控喚醒免疫系統治療轉移性黑色素癌

Synergistic effect of novel light-driven drugs and paclitaxel: awakening the immune system through gene regulation for the treatment of metastatic melanoma

王惠民/國立中興大學生醫工程研究所/教授
李旭東/臺中榮總整合性癌症中心/主任

在這項研究中，北冬蟲夏草 (Cordyceps militaris (Linn.) Link (CM)) 的水提取物被用作材料，以研究其對 B16F10 和 lung metastatic melanoma (LMM)細胞的抑制機制。我們將還原力、螯合能力和 2-diphenyl-2-picrylhydrazyl (DPPH) 測定應用於抗氧化能力，並從適當濃度的CM中獲得了令人滿意的結果。為了檢查CM在黑色素瘤增殖抑制中的能力，且證實之前的結果，再通過(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, MTT)測定、細胞遷移和侵襲評估。藉由雙方單位的合作，本研究表明，CM 具有多種生物學功能，包括抗氧化、抗腫瘤、抑制腫瘤侵襲和促進 T 細胞免疫毒性細胞的活性。

In this study, the water extract of Cordyceps militaries (Linn.) Link (CM) was used as a functional material to investigate the inhibitory mechanisms on B16F10 and lung metastatic melanoma (LMM) cells. Reducing power, chelating ability, and 2-diphenyl-2-picrylhydrazyl (DPPH) assays were applied for antioxidative capacities, and we obtained positive results from the proper concentrations of CM. To examine the ability of CM in melanoma proliferation inhibition and to substantiate the previous outcomes, three cellular experiments were performed via 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, MTT, a tetrazole) assay, cell migration, and invasion evaluation. This study showed that CM exhibits various biological capabilities, including antioxidation, antitumor, tumor invasion suppression, and T cytotoxic cell activity promotion.

TCVGH-NCHU1117612

高尿酸血症/痛風與骨質疏鬆間其單核苷酸多型性的相關性研究

Association between gout/hyperuricemia and osteoporosis in relation to single nucleotide polymorphism

施因澤/國立中興大學應用數學系(所)/教授
張雁霖/臺中榮民總醫院藥劑部/藥師
廖勇柏/中山醫學大學公共衛生學系(所)/教授

骨質疏鬆被世界衛生組織認為盛行率僅次於心血管疾病，造成龐大的醫療支出以及可能造成年老者失能，是重要的公共衛生議題。目前雖已經有研究針對痛風與骨質疏鬆經由機制及流行病學角度進行討論，但對於此兩者間相關性結論卻仍不一。因此本研究將利用臺灣人體生物資料庫蒐集之骨質疏鬆、問卷、身體檢測、血液尿液檢驗，調整個人生活習慣或其他常見共病等因子後，對於痛風與骨質疏鬆之間的相關性進行探討。

結果中發現臺灣人群中痛風和運動對於骨質疏鬆具有交互作用，而痛風、運動分別與降低骨質疏鬆風險有關，皆達到統計上顯著。在分層分析後，僅在有規律運動組中，痛風與較低骨質疏鬆風險較低相關，在無規律運動中則沒此現象。另外，若以無痛風、無規律運動做為參考組，有規律運動的人不論有無痛風，皆與骨質疏鬆風險較低相關。

Osteoporosis is a major public health issue and is considered by the World Health Organization as the second most prevalent disease. Studies from both mechanistic and epidemiological perspectives have reported varying results on the correlation between gout and osteoporosis. Thus, the conclusions remain inconsistent. In this project, the correlation between gout and osteoporosis in relation to personal habits and other common co-morbidities will also be considered. Data were collected using questionnaires, biochemical tests, and physical examinations will be retrieved from the Taiwan Biobank.

From results, we found out an interaction of gout, exercise and osteoporosis. Both gout and exercise habit were associated with lower risk of osteoporosis and reached statistical significant. In the stratification analysis, gout was related with lower risk to osteoporosis only in regular exercise people but not no-exercise. Moreover, using no-exercise and without gout as reference group, people exercise regularly had a lower risk to osteoporosis whether they have gout or not.

TCVGH-NCHU1117613

特異性促消退因子在抗磷脂抗體症候群致病機轉扮演的角色

The role of specialized pro-resolving mediators in the pathogenesis of antiphospholipid antibody syndrome

賴建成/國立中興大學分子生物學研究所/教授
譚國棟/臺中榮民總醫院過敏免疫風濕科/主治醫師

背景
抗磷脂抗體症候群是一種常見的自體免疫疾病，與全身性紅斑性狼瘡相關，其特色是產生β2-糖蛋白 I 依賴性抗磷脂質自體抗體，以及動脈或靜脈血栓生成或產科併發症。目前的治療策略主要依賴抗血小板藥物和抗凝血劑治療，這會增加出血的風險。一群脂質媒介（專門的促緩解媒介因子，SPM）有助於緩解人體內的發炎反應。缺乏 SPM 與一些自體免疫疾病的產生有關。
方法
我們招募了沒有活動性血栓事件的原發性抗磷脂抗體症候群門診患者和健康對照組。我們透過 LC-MS-MS 在研究參與者中測量 SPM 的血漿濃度，以發現抗磷脂抗體症候群病患中下降的 SPM。Mann-Whitney U 檢驗用於組間的比較。
結果
我們招募了 17 名原發性抗磷脂抗體症候群患者和 32 名健康對照者。我們的結果顯示抗磷脂抗體症候群患者和健康對照組之間有一些差異表現的 SPM。特別是，與健康對照組相比，原發性抗磷脂抗體症候群患者血中的 18R/S-HEPE 和 5S、15S-diHETE 降低。
結論
總結來說，與健康對照組相比，我們在抗磷脂抗體症候群患者中發現了幾種差異表現的血漿 SPM。在得出結論之前需要進行進一步的驗證實驗和機轉研究。

關鍵詞: 抗磷脂抗體症候群; 專門的促緩解媒介因子

Background
Antiphospholipid antibody syndrome (APS), an autoimmune disease frequently associated with systemic lupus erythematosus (SLE), is characterized by the production of β2-glycoprotein I (B2GPI)-dependent antiphopholipid autoantibodies (aPL), and arterial or venous thrombotic events or obstetrical complications. The current treatment strategy primarily relies on the administration of antiplatelet agents and anticoagulants, which carries an increased risk of hemorrhage. A group of lipid mediators (specialized pro-resolving mediators, SPMs) contribute to the resolution of inflammation in the human body. Lack of SPMs has been implicated in the generation of several autoimmune diseases.
Methods
We enrolled primary APS outpatients without active thrombotic events and healthy controls.

Plasma levels of SPMs are measured by LC-MS-MS in study participants to find down-regulated SPMs in APS patients. The Mann-Whitney U test was used to for between-group comparisons.

Results

We recruited 17 primary APS patients and 32 healthy controls. Our results demonstrated several differentially expressed SPMs among APS patients and healthy controls. In particular, 18R/S-HEPE and 5S, 15S-diHETE decreased in primary APS patients when compared with healthy controls.

Conclusions

In conclusion, we found several differentially expressed plasma SPMs in APS patients when compared with healthy controls. Further validation experiments and mechanistic studies are required before the conclusion is made.

Keywords：antiphospholipid antibody syndrome; specialized pro-resolving mediators

TCVGH-NCHU1117614

探討香杉芝萃取物經由抑制STAT3活化而影響攝護腺癌細胞的上皮間葉轉變及癌幹特性

The effect of Antrodia salmonea extract on the epithelial-mesenchymal transition and cancer stemness propoerties in human prostate cancer through STAT3 regulation

林赫/國立中興大學生科系/特聘教授兼系主任
王心怡/台中榮總核醫科/主治醫師
Ayse Celik/中興大學生科系/研究生

香杉芝 (Antrodia salmonea, AS)為台灣原生種的菌類，具有抗氧化、抗發炎與抗癌症等效用。我們的近期研究表明 AS 對於許多癌細胞具有抗癌的功能。然而，AS 在前列腺癌細胞於幹性 (stemness)與上皮間質轉化 (epithelial-mesenchymal transition ,EMT) 的功能尚不明確。在此研究中，我們目標探討於前列腺癌細胞進程中，AS 是否藉由調控 STAT3 蛋白表現而影響其幹性與上皮間質轉化。我們的初步結果顯示，隨著濃度的上升，AS 能顯著抑制人類前列腺癌細胞株的增生。此外，AS 所引起的前列腺癌細胞增生抑制作用導致了 STAT3 蛋白的表現與其磷酸化位點 Ser727 活化程度下降。另外，AS 能抑制 EMT 指標蛋白 N-cadherin，且促進前列癌細胞的凋亡。初步結果推測 AS 可能為適宜治療前列腺癌的候選藥物。為了詳細地探討 AS 對於前列腺癌細胞進程的影響，本計畫設立三個主要的研究目標：1. 探討針對前列腺癌細胞增生研究的 AS 藥物濃度與訂定針對正常前列腺細胞無毒性的安全劑量。2. 探討 AS 對於前列腺癌細胞爬行與侵襲的適宜藥物濃度。3. 探討 AS 於前列腺癌細胞幹性和上皮間質轉化的角色。本研究的預期結果將表明 AS 對於治療前列腺癌細胞的訊息傳遞機制。最後，我們預期將此計畫結果完善整理與投稿至 SCI 期刊，以作為本研究的最終目的。

Antrodia salmonea (AS) is a fungus, which belongs to a fungal family of Taiwanofungus salmoneus with the features of anti-oxidant, anti-inflammatory, and anticancer. Our recent studies have shown that AS has anti-cancer functions in multiple types of cancer. However, the effects of AS on prostate cancer (PCa) stemness and epithelial-mesenchymal transition (EMT) remain unknown. In this proposal, we aim to investigate the role of AS in prostate cancer progression through STAT3 regulation along with cancer stemness and EMT. Our preliminary data show that AS significantly inhibits prostate cancer cell proliferation in a dose-dependent manner in human prostate cancer cell lines. Besides, AS-inhibited prostate cancer proliferation results in a decreased protein expression level of STAT3 and its activation by inhibiting p-Ser727 STAT3. In addition, AS inhibits EMT marker N-cadherin, and promotes prostate cancer cell apoptosis. Our preliminary results suggest that AS may be a good candidate for the treatment of prostate cancer. In order to investigate more detailed functions of AS in prostate cancer progression, we propose three main aims in this project: 1. Investigation of AS concentration on prostate cancer proliferation and identify the appropriate dose that is not

toxic for the healthy prostate cells but only effective for prostate cancer cells. 2. Investigation of the role of AS with an appropriate concentration on prostate cancer cell migration and invasion. 3. Investigation of the role of AS on EMT and cancer stemness in prostate cancer cells. This proposal comes along with expected outcomes indicating the potential treatment strategies and detailed signaling mechanisms for prostate cancer treatment. Eventually, we will prepare a good-quality manuscript and publish our results in an SCI journal at the end of this study.

TCVGH-NCHU1117615

篩選食品潛力成分探討其對大腸直腸癌生長之影響

Effects of selected potential compounds in foods on the growth of colorectal cancer

林金源/國立中興大學食品暨應用生物科技學系/教授
陳周誠/台中榮民總醫院大腸直腸外科/主治醫師
吳亭儀/國立中興大學食品暨應用生物科技學系

咖啡酸為植物中常見的酚酸化合物，已有許多研究指出其具有抗發炎及抗癌的潛力，但其衍生物之完整研究則較少，因此本研究目的是為瞭解咖啡酸及其衍生物之抗發炎作用，進而篩選出抗發炎潛力物質以探討其抗大腸癌細胞生長之功效。本研究選用咖啡酸(CA)、單咖啡醯奎尼酸 (Caffeoylquinic acid, CQA) 4 種及雙咖啡醯奎尼酸(Dicaffeoylquinic acid, DCQA) 6 種，合計咖啡酸及其衍生物共 11 種為樣品。確定樣品各自對 BALB/c 雌鼠初代腹腔巨噬細胞無毒性之劑量後，分成樣品與細胞直接培養及樣品和脂多醣與細胞共同培養方式，探討其抗發炎潛力，收集細胞培養液，利用酵素免疫連結分析法，測定其促發炎(TNF-α、IL-1β、IL-6)與抗發炎(IL-10)細胞激素分泌量之變化，再以多變量分析之主成分分析法(PCA)分析樣品添加對細胞激素分泌量之貢獻，以篩選出抗發炎潛力物質。結果顯示，在直接與樣品作用模式中，咖啡酸及其衍生物皆能增加促發炎激素的分泌，證明咖啡酸及衍生物具有刺激巨噬細胞之活性；與脂多醣共同培養模式中，發現 CA 及 CQA 能夠降低 TNF-α、IL-1β及增加 IL-10 的分泌。藉由主成分分析發現 CA 及 5-CQA 降低促發炎和增加抗發炎細胞激素之分泌效果較為明顯，推測所選取的 11 種咖啡酸及其衍生物中，以 CA 及 5-CQA 最具有抗發炎之潛力。

將篩選所得之抗發炎樣品 CA 及 5-CQA，利用直接添加及免疫療法方式，來評估其對人類大腸癌 HT-29 細胞生長之影響。結果顯示，直接添加 CA 及 5-CQA 經培養 24 及 48 小時，皆能顯著降低人類大腸癌 HT-29 細胞存活率，而在免疫療法模式下，經培養 24 及 48 小時，也皆能顯著降低人類大腸癌 HT-29 細胞存活率，證實 CA 及 5-CQA 可經由直接及免疫療法模式抑制大腸癌細胞之生長。

關鍵詞: 抗發炎、咖啡酸、咖啡酸衍生物、癌症免疫療法、細胞激素、人類大腸癌 HT-29 細胞

Caffeic acid is a common phenolic acid compound in plants. Many studies have supported that caffeic acid has anti-inflammatory and anti-cancerous potential. However, there are limited researches about caffeic acid derivatives. To clarify the puzzle, the purpose of this study is to understand anti-inflammatory effects of caffeic acid and its derivatives and then explore their effectiveness of anti-cancer activity. A total of 11 kinds of caffeic acid and its derivatives were selected for this study, including caffeic acid (CA), 4 kinds of caffeoylquinic acid (CQA) and 6 kinds of dicaffeoylquinic acid (DCQA). The non-cytotoxic doses of each individual sample to the growth of primary peritoneal macrophages from female BALB/c mice

were determined by MTT assay. Then, two models were used to evaluate the anti-inflammatory effectiveness by samples in the absence or presence of lipopolysaccharide (LPS). The levels of pro-inflammatory (TNF-α, IL-1β, IL-6) and anti-inflammatory (IL-10) cytokines secreted by macrophages were analyzed by enzyme-linked immunosorbent assay (ELISA). Cytokine secretions contributed by each individual sample were analyzed by principal component analysis (PCA) to select potent anti-inflammatory compounds. The results showed that caffeic acid and its derivatives increased the secretions of pro-inflammatory cytokines by macrophages in the absence of LPS, evidencing that caffeic acid and its derivatives have the stimulatory activity to macrophages in the direct interaction mode. On the other hand, it was found that CA and CQA decreased the secretions of TNF-α and IL-1β but increased the secretion of IL-10 by macrophages in the presence of LPS. Using PCA, CA and 5-CQA were found to have the most significant effects for reducing the secretions of pro-inflammatory cytokines but increasing the secretion of anti-inflammatory cytokine. Therefore, CA and 5-CQA were selected as potent anti-inflammatory compounds for the following anti-cancer study.

The potent anti-inflammatory samples, CA and 5-CQA, were used to treat human colorectal cancer HT-29 cells with direct addition and indirect immunotherapy using conditioned media of primary peritoneal macrophages for 24 and 48 hours. The results showed that CA and 5-CQA significantly reduced the survival rate of human colorectal cancer HT-29 cells. It is proved that CA and 5-CQA inhibit the growth of colorectal cancer cells through direct addition and indirect immunotherapy.

Keywords：Anti-inflammation, Caffeic acid, Caffeic acid derivatives, Cancer immunotherapy, Cytokines, Human colorectal cancer HT-29 cells

TCVGH-NCHU1117616

以犬乳腺癌細胞模式探討蛋白質二硫鍵異構酶AGR2所調控之分泌蛋白體與腫瘤轉移的關聯

Investigating the protein disulfide bond isomerase AGR2-regulated secretome and its association with tumor metastasis using canine mammary tumor cells

劉浩屏/國立中興大學獸醫學系(所)/副教授
楊陽生/臺中榮民總醫院血液腫瘤科/主治醫師
阮賢齊/國立中興大學獸醫學系(所)/學生

犬乳腺癌是雌性犬好發的惡性腫瘤，許多特徵與人乳癌近似，後期預後不佳。我們發現 AGR2 過度表現於犬乳腺癌組織。AGR2 為內質網的蛋白質二硫鍵異構酶，參與維持內質網內蛋白質的恆定。AGR2 亦可被分泌到細胞外(eAGR2)，具有不同於其內質網功能的促癌作用。我們已證明乳腺癌患犬血清 AGR2 濃度與腫瘤遠端轉移、治療反應及總生存率不佳顯著相關，但仍不了解調節 AGR2 分泌的機制以及 eAGR2 對犬乳腺癌的影響。我們發現犬乳腺癌細胞大量表現 AGR2 時，能促使 AGR2 分泌至細胞外，並改變細胞分泌體以吸引犬乳腺癌細胞的趨化性遷移。我們以蛋白質體學技術鑑定出 14-3-3ε 及 ACTN4 受 AGR2 調節釋放至細胞外；在基因靜默或基因剔除 AGR2 後，犬乳腺癌細胞株分泌體中 14-3-3ε 及 ACTN4 含量顯著下降，吸引犬乳腺癌細胞的趨化性的程度亦降低。加入 14-3-3ε 或 ACTN4 之專一性抗體亦弱化分泌體對癌細胞之趨化能力。此外，我們發現內質網壓力能促使 AGR2 的表現量增加，並促進 14-3-3ε 及 ACTN4 釋放至細胞外。本計畫首度揭示 AGR2 與應激反應、細胞外 14-3-3ε 及 ACTN4 之間的相互影響，後續研究將有助於增進對腫瘤的瞭解及優化治療策略。

關鍵詞: 犬乳腺癌、前梯度蛋白 2(AGR2)、內質網、分泌體、促癌、趨化性、抗藥性

Canine mammary tumors (CMT) are the most prevalent neoplasms in female dogs bearing clinicopathologic features in common with human breast cancers. We previously identified that anterior gradient 2 (AGR2) is overexpressed in CMT tissues. AGR2 acts as a protein disulfide isomerase (PDI) maintaining the proteostasis in the endoplasmic reticulum (ER) and likely exerts pro-oncogenic effects through regulating the processing or secretion of pro-tumorigenic proteins. AGR2 is also secreted outside the cell and extracellular AGR2 (eAGR2) has distinct pro-oncogenic functions independent of its PDI activity. We previously evidenced that the serum eAGR2 concentration is significantly associated with distant tumor metastases, adverse treatment responses and poor overall survival of CMT dogs. We further demonstrated that the spent conditioned media of AGR2-expressing CMT cells can drive CMT cell chemotaxis. Depletion of eAGR in the media did not completely block the chemotaxis effect. Moreover, supplementation of recombinant AGR2 into spent culture media, but not fresh culture media, can confer the cell chemotaxis effect, suggesting that eAGR2 likely

modulates pro-chemotaxis components in the extracellular microenvironment of CMT cells. To identify the AGR2-modulated extracellular proteins, we exploited one-dimensional gel electrophoresis coupled with liquid chromatography-tandem mass spectrometry (GeLC-MS/MS) to analyze the secretomes collected from two CMT cell lines expressing ectopic AGR2 versus the respective vector control. A list of proteins differentially present in the secretome of AGR2-expressing cells were identified. Among them, 14-3-3ε and alpha actinin 4 (ACTN4) are top proteins with increased abundance in the secretome of AGR2-expressing cells in both CMT cell lines. We validated that protein abundance of 14-3-3ε and ACTN4 was elevated in the media of AGR2-expressing CMT cells. In contrast, extracellular 14-3-3ε and ACTN4 levels were significantly decreased in the media of AGR2-knockdown or AGR2-knockout CMT cells, in conjunction with a reduced cell chemotaxis effect of the media. Importantly, specific antibodies against 14-3-3ε or ACTN4 significantly impaired the chemotaxis effect of the media. Our present data reveal that AGR2 can enhance the externalization of 14-3-3ε and ACTN4 together with eAGR2 to drive cell chemotaxis. Further investigation will unveil the interplay between AGR2, stress response, and extracellular pro-oncogenic functions of 14-3-3ε and ACTN4 in CMT, which also serves as a translational model advancing the understanding and therapy strategies of human cancers.

Keywords：canine mammary tumor (CMT), anterior gradient 2 (AGR2), endoplasmic reticulum (ER), secretome, pro-oncogenic, chemotaxis

TCVGH-NCHU1117617

製備含薑黃素與肝素之強韌型水凝膠及其應用

Preparation and application of tough hydrogel containing curcumin and heparin

黃智峯/國立中興大學化學工程學系/教授
王中琦/台中榮民總醫院心臟血管外科/醫師
林鼎智/國立中興大學化學工程學系

我們透過兩步聚合法來製備雙網絡水凝膠(Double network hydrogels，DN)，在第一網絡(1st Network)的設計中，我們以 AMPS (2-Acrylamido-2-methylpropane sulfonic acid)與 DMAA (N,N'-Dimethylacrylamide)進行共聚，由於 DMAA 與過硫酸鹽在熱聚合過程中會產生自交聯(Self-crosslinking)反應，因此我們利用此機制來增加 1st Network 犧牲鍵含量以提升 DN 的韌性。自交聯機制與傳統交聯劑不同，由於傳統交聯劑具有兩個以上 Acrylic group，導致聚合時容易產生交聯網絡過於密集的問題，而自交聯機制則是使 DMAA 叔胺上的甲基生成一自由基，後續與單體形成交聯網絡或者鏈增長，使 SN 在增加犧牲鍵的同時仍具有一定的溶脹能力。

我們藉由 Cryo-SEM/TGA/DSC/DMA 對單網絡水凝膠(Single network hydrogels，SN/DN 之微結構/熱性質/黏彈性進行分析，以證實自交聯網絡的生成和 SN/DN 結構的變化，之後再利用材料試驗機進行機械性質分析。最後我們將微胞化薑黃素(Micellar-Cur)導入 DN 中做為搭載藥物，利用吸收度檢驗 Cur-DN 於 PBS (Phosphate-buffered saline)溶液中之藥物釋放能力並分析其釋放模型，以及將 Cur-DN 與大腸桿菌及金黃色葡萄球菌進行抑菌圈測試，觀察其抗菌能力，最後我們得到具有優秀機械性能($\sigma T \approx 1.8$ MPa; $\varepsilon T \approx 190\%$)、藥物釋放能力(釋放率 ≈25%)、抗菌能力(金黃色葡萄球菌)之 DN。

We prepared double network hydrogels (DN) by a two-step polymerization method. In the design of the 1st Network, we copolymerized with AMPS (2-acrylamido-2-methylpropane sulfonic acid) with DMAA (N,N'-dimethylacrylamide), due to DMAA with persulfate produces a self-crosslinking reaction during thermal polymerization. We use this mechanism to increase the sacrificial bond content of the 1st Network. The self-crosslinking mechanism is different from the traditional crosslinking agent to make the methyl group on the DMAA tertiary amine produce a free radical to make the monomer polymerize, then form a crosslinking network or chain growth. Accordingly, it still has a certain degree of swelling ability while increasing the sacrificial bond. We analyze the morphology/thermal properties/viscoelasticity of single network hydrogels SN/DN by Cryo-SEM/TGA/DSC/DMA to confirm the generation of self-crosslinking networks and the changes in SN/DN structure, and then use material testing machines for mechanical property analysis.

We introduced micellization curcumin (Micellar-Cur) into DN as a drug, used the absorption to test the drug release ability of Cur@DN in PBS (phosphate-buffered saline) solution, analyzed its release model, and tested Cur-DN with E.coli and Staphylococcus aureus

to observe its antibacterial ability. Finally, we obtained excellent mechanical properties ($\sigma T \approx$ 1.8 MPa; $\varepsilon T \approx$ 190%), drug release behavior (release percentage $\approx$ 25%), and antibacterial activity (Staphylococcus aureus) of our DNs.

TCVGH-NCHU1117618

利用持續性生理監測穿戴裝置、影像人工智慧演算法及心肺復健評估發展慢性肺病之長期預測及智能照護模組

Using continuous physiological monitoring wearable devices, image artificial intelligence algorithms and cardiopulmonary rehabilitation assessment to develop long-term prediction and intelligent care models for chronic lung disease.

傅彬貴/臺中榮總間質性整合照護中心/主任
吳俊霖/國立中性大學資訊與工程學系/教授兼系主任
程遠揚/臺中榮總復健醫學科/主任

本計畫以罹患肺纖維化疾病之病人為研究標的，於臺中榮總間質性肺病整合照護中心發展一個動態量測罹患間質性肺病病人生理指標的場域，此外，也與中興大學資訊工程學系吳俊霖教授團隊發展間質性肺病肺部影像學之人工智慧演算法模組。因此，本研究計畫的內容分成兩大部分，第一部分是標準化動態生理量測模組，包含六分鐘走路測試、心肺運動測試，並在受試者行走時，以攝影方式獲取其步態、移動速度等參數，並與間質肺病之生理參數 GAP score (Gender, age and pulmonary function test)建立相關性，並探討生理量測參數與 GAP score 之相關性。第二部分是使用間質性肺病病人高解析度電腦斷層影像進行病灶標誌，並由中興大學團隊進行機器學習以建立人工智慧影像辨識，期能透過機器學習在影像辨識以及分割的技術逐漸成熟，讓過電腦自我學習，根據肺部高解析電腦斷層來判斷纖維化的病情，進而輔助醫師進行診斷。

在第一部份的結果，子計畫一，我們總共分別收入了 71 位受試者進行穿戴式生理裝置與動態量測，以探討動態生理參數與肺纖維化病人肺功能之相關性。初步結果顯示，受試者的年齡中位數 63 歲 (IQR: 53-72)，GAP score 為 2.0 (IQR: 1-3), 最大吐氣量 FVC (%)為 74% (61-90%) 以及一秒吐氣量 FEV1(%)為 75% (54-88%)。在六分鐘走路測試前，血氧濃度為 96.0 % (96-97.5%)，在走完六分鐘後，血氧濃度為 93.0% (87-96%)，最低血氧濃度為 89.0% (82-93%)。六分鐘內行走距離中位數為 423 公尺(351.5-486)，在行走前的喘促分數為 1.0 (0-2)，在行走後的喘促分數為 4.0 (2-5)。進行了相關性分析檢定，結果發現生理訊號當中的灌流指數與受試者肺功能檢查當中的 FVC (%)、FEV1(L)、 FEV1(%) 以及完成走路後的喘促分數具有顯著統計之相關性，相關係數分別為 FVC(%): r = 0.25、FEV1(L): r = 0.27、FEV1(%) : r = 0.33 以及 Borg Scale: r = -0.35。此外，也發現 GAP score 與六分鐘走路測試後之生理訊號具有顯著負相關性，其中舒張壓 r = -0.33、心律 r = -0.36、最大心律 r = -0.53。子計畫三，我們也對 65 位肺纖維化受試者，進行 GAP score 與人工智慧移動影像分析技術及六分鐘運動生理參數之相關性。人工智慧影像分析係以兩個不同方向獲取的影像資料，分別為與病人行走之水平影像與垂直影像。總共有五個生理參數被發展於影像辨識系統，分別為步速(rhythm，單位：step/sec)、最大步距(Maximum stride，單位：m), 移動速率(moving speed，單位：m/sec)、身體前傾角度(forward leaning angle)、平均關節擺動角度(average shoulder angle)。以相關係數進行統計，結果發現 GAP score 顯著與最大步距呈現顯著負相關 r = -0.39；與移動速率呈現顯著負相關 r = -0.42。

第二部分，基於深度學習使用分割的方式來診斷纖維化，關於模型整體的配置需要

透過反覆的試錯過程進行人工的調整，不僅費時且通常僅能找到次佳解。本計畫提出了一個使用基於自配置機制的深度神經網路來分割肺部纖維化的方法，旨在根據數據集屬性自動配置最適合的網路架構並添加深度監督以提升網路的性能。本計畫所提方法對於分割肺部纖維化有良好的表現，在評估指標 Dice coefficient 中分別提升了 0.92%及 0.61%。在較困難的影像如小範圍的纖維化、邊緣，仍可精確分割。

關鍵詞: 肺部纖維化、深度學習、電腦視覺、自配置、深度監督；心肺運動測試、六分鐘走路測試、人工智慧移動影像分析技術

The purpose of this project is to develop a method for dynamically measuring the physiological indicators of patients with interstitial lung disease in the Interstitial Lung Disease Integrated Care Center at Taichung Veterans General Hospital (TCVGH) , which uses patients suffering from pulmonary fibrosis as its research subject. It also cooperates with the Department of Computer Science and Engineering at Chung Hsing University (NCHU). Professor Wu from the Department of Computer Science and Engineering developed an artificial intelligence algorithm module for lung imaging of interstitial lung disease. As a result, this project is divided into two parts. The first part of the study is a standardized dynamic physiological measurement module, which consists of a six-minute walk test and a cardiopulmonary exercise test. When the subjects are walking, their gait, parameters such as moving speed, and establish a correlation with the physiological parameter GAP score (Gender, age and pulmonary function test) of interstitial lung disease and investigate if physiological measurements and GAP scores are correlated. Secondly, high-resolution computed tomography (HRCT) images of patients with interstitial lung disease will be used to detect lesions, and Professor Wu is using machine learning to achieve artificial intelligence image recognition. Machine learning is expected to gradually mature the technology of image recognition and segmentation. Computers can learn by themselves, evaluate lung fibrosis using HRCT, and assist doctors in diagnosing patients.

In the first part of this project, we prospectively enrolled patients who were diagnosed as fibrotic lung disease into this study. Patient who has a resting oxygen level more than 95% and could tolerate with 6MWT was recruited. A Bluetooth ear-hook device was used to monitor five physical parameters, such as blood pressure, body temperature, heart rate, oxygenation level and perfusion index (PI) during 6MWT. Spearman's rank correlation coefficient was applied to analyze the correlation. A total of 71 patients were enrolled into study and completed the analysis. The demographic data showed age was 63 (IQR: 53-72), GAP score was 2.0 (1-3), FVC (%) was 74% (61-90%) and the FEV1(%) was 75% (54-88). The 6MWT showed SaO2 in pretest was 96.0 % (96-97.5), SaO2 in posttest was 93.0% (87-96) and nadir 89.0% (82-93); the distance was 423 meters (351.5-486); and Borg Scale was 1.0 (0-2) in pretest and 4.0 (2-5) in posttest. From the Spearman`s rank correlation test, we found that perfusion index was significantly correlated to FVC (%), FEV1(L), FEV1(%) and Borg Scale

after 6MWT with a Spearman's rho was 0.25, 0.27, 0.33 and -0.35, respectively. The GAP score was significantly negative correlated to diastolic blood pressure, heart rate and maximal heart rate after 6MWT with a Spearman's rho was -0.33, -0.36, and -0.53, respectively.

In addition, we also prospective study enrolled 65 patients who were diagnosed as fibrotic lung disease into the gait analysis research. Patient who has a resting oxygen level more than 95% and could tolerate with 6MWT was recruited. An artificial intelligence (AI) gait image analysis system was conducted by using two cameras positioned in two different directions to capture images of patients during walking. Spearman's rank correlation coefficient was applied to analyze the correlation. The chi-square test was used to analyze discrete variables. A total of 65 patients were enrolled into analysis. Five parameters were defined by using AI gait image analysis system, which includes rhythm (step/sec), maximum stride (m), moving speed (m/sec), Joint swing angle analysis of forward leaning angle and average shoulder angle. From the Spearman`s rank correlation test, we found that GAP score was significantly correlated to maximum stride and moving speed with a Spearman's rho was -0.39 and -0.42, respectively. In the comparison of GAP I & II-III, higher GAP score was also significantly decreased in maximum stride and moving speed.

In the second part, we were focusing on the image analysis of HRCT from patient who were diagnosed as fibrotic lung disease. The previous method used computed tomography and relaxed examinations to diagnose pulmonary fibrosis by professionals. With the gradual maturity of machine learning in image recognition and segmentation, it is expected that computer self-learning will be used to diagnose pulmonary fibrosis based on computed tomography, and then assist physicians in diagnosis. However, to diagnose pulmonary fibrosis using segmentation based on deep learning, the overall configuration of the model needs to be manually adjusted through an iterative trial and error process, which is not only time-consuming but usually only finds suboptimal solutions. This study proposed a method to segment pulmonary fibrosis using a deep neural network based on a self-configuration mechanism, aiming to automatically configure the most suitable network architecture according to the properties of dataset and add deep supervision to improve the performance of the network. The method proposed in this study has a good performance in segmentation of pulmonary fibrosis which respectively increased 0.92% and 0.61% in the evaluation metrics and it can still be accurately segmented in difficult images, such as small area and edge of pulmonary fibrosis.

Keywords：Pulmonary Fibrosis, Deep Learning, Computer Vision, Self-Configuration, Deep Supervision、Cardiopulmonary Exercise Testing(CPET)、Six Minute Walk Test (6MWT)、Artificial Intelligence (AI) Gait Image Analysis System

榮靜計畫

TCVGH-PU1118101

以邊緣智慧技術達成高品質急救教學即時回饋

Real-time Feedback System on Training for High Quality Resuscitation with Edge AI Technology

詹毓偉/靜宜大學資訊學院/副教授
詹毓哲/臺中榮民總醫院職業醫學科/主任
楊朝棟/東海大學資訊工程系/終生特聘教授
張志宏/靜宜大學資訊學院/副教授
蔡英德/靜宜大學資訊學院/教授
胡松原/臺中榮民總醫院急診部/科主任
林承賦/臺中榮民總醫院高齡醫學中心/主治醫師
詹惟臣/臺中榮民總醫院/研究助理
林彥亨/靜宜大學資訊學院/研究助理

「緊急醫療」為針對有急性疾病或緊急創傷，需要立即進行醫療救治的病患。急診專科醫師則須在第一時間需穩定病患，使其有機會接受後線次專醫師進一步治療。然而在緊急搶救過程中，有些因嚴重疾病或重大意外病患已達心跳停止，此時心肺復甦術(Cardio-Pulmonary Resuscitation，CPR) 是必要且迫切的一種急救措施。如何有效地教導與訓練學習者達到高品質CPR的目標，若單靠CPR的合格指導員仍顯不足。因此，開發具自動智慧判斷與導引功能之教學回饋系統顯得格外重要。基於去年計畫之研發成果，今年的計畫結合『邊緣智慧(Edge AI)』架構建構以邊緣智慧為基礎之CPR即時辨識與教學回饋系統，讓機器得以自動判斷CPR學習者動作，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。本計畫透過OpenPose人體姿態估計技術成功建置(A)標準化之邊緣智慧CPR系統環境建置。(B)Android版本之應用程式(App)。首先，目前已完成標準化邊緣智慧CPR系統建置，可以針對學員在CPR教學環境中的擺位姿勢、按壓深度、按壓頻率及按壓位置進行判斷並給予即時文字和語音回饋。未來將持續優化此系統並完成Android版本之應用程式。

"Emergency medicine" is for patients who have illnesses or injuries and require immediate cure. Emergency doctors are responsible for diagnosing and treating urgent patients and coordinating treatment with specialty doctors, as well as determining how patients need to be admitted, observed or discharged. However, in emergency medicine, Cardio Pulmonary Resuscitation (CPR) is usually a necessary and urgent first aid measure for patients whose heart stops beating due to diseases or accidents. How to effectively teach and train learners to achieve the goal of high quality CPR is still insufficient if we rely solely on qualified CPR instructors. Therefore, it is particularly important to develop a teaching feedback system with

automatic intelligent judgment and guidance functions. Based on the results of last year's project, in this year, the "Edge AI" architecture is combined to build a CPR real-time recognition and teaching feedback system based on edge intelligence, so that the machine can automatically determine whether the CPR learner's movements meet the requirements of high-quality CPR and provide real-time teaching feedback, so that CPR learners can follow the feedback instructions and correct the wrong posture in real time This allows CPR learners to correct their posture errors in real time according to the feedback instructions and gradually practice to achieve the goal of high quality CPR. This project has successfully built (A) a standardized edge smart CPR system environment through OpenPose human posture estimation technology. (B) Android version of the application (App). First of all, the standardized edge smart CPR system has been built, which can judge and give real-time text and voice feedback to the trainee's posture, pressing depth, pressing frequency and pressing position in the CPR teaching environment. In the future, we will continue to optimize the system and complete the Android version of the application.

TCVGH-PU1118102

紅藜對肌少症與相關調控分子機制之影響

Effects of *Djulis* on sarcopenia and related molecular signaling

詹吟菁/靜宜大學食品營養系/特聘教授
李奕德/臺中榮民總醫院/新陳代謝科主任
廖玉惠、林思佳、黃珍琳/靜宜大學食品營養系/碩士生及大學部學生

肌少症(Sarcopenia)是一種肌力下降及肌肉質量降低的徵狀，是引起老年人失能、住院、死亡的的重要因素，如何有效預防及治療肌少症為高齡化社會極重要的議題。紅藜(*Djulis*)是台灣原生種植物，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、緩解代謝症候群症狀、調節免疫及保護大鼠免受CCl_4造成的肝損傷等作用。在我們先前的研究結果顯示紅藜可提高SAMP8小鼠腦部沉默調節蛋白(silence information regulator 1, Sirt 1)表現量，抑制哺乳動物雷帕黴素目標蛋白(Mammalian target of rapamycin, mTOR)及P70S6激酶(P70 S6 kinase, P70S6K)的磷酸化，增強自噬活化因子Beclin 1及微管相關蛋白輕鏈3 II(Microtubule-associated protein light chain 3-II, LC3-II)的表現，進而緩解了學習記憶能力的缺損。紅藜還可提升肝臟的自噬作用，降低凋亡反應及GPT含量，並改善脂肪肝指數，然紅藜對老化所伴隨的肌少症及相關的調節機制則尚不清楚。因此，本次計畫擬探討紅藜對老化肌少症動物模式SAMP8小鼠肌肉質量及肌力，與蛋白合成跟降解相關可能調控路徑之影響。將3月齡SAMP8小鼠為實驗對象，分為對照組及添加不同劑量的紅藜組，進行12週。犧牲前進行肌力測試，犧牲後取肌肉檢體秤重，並分析肌肉蛋白合成相關訊息因子及肌肉降解途徑。結果顯示，紅藜可藉由活化肌肉中mTOR來抑制自噬因子Beclin-1，降低LC3-II，而達到減緩肌肉降解，且在Sirt 1也有下降的趨勢。另外，在肌肉合成的部分，AKT及P70S6K則無顯著差異。綜合上述結果得知，紅藜可能透過緩解肌肉降解的路徑來改善肌肉量及肌力，進而延緩老化所導致的肌少症之進展。

關鍵詞：肌少症、紅藜、肌肉質量、肌力、蛋白合成、自噬

Sarcopenia is characterized with reduced muscle strength and muscle mass, and is an important factor to induce dysfunction, hospitalization and mortality for the elderly. *Djulis* is a native plant of Taiwan. It contains abundant active components, could reduce oxidative stress by enhancing antioxidantion and suppressing apoptosis. *Djulis* also has many beneficial effects, such as anti-fatigue, lowering lipids, improving metabolic syndrome symptoms, regulating immune function, and protecting liver from the CCl4 induced damage. Our previous studies demonstrated that *Djulis* increased the expressions of silent regulatory protein (Sirt 1), inhibited the phosphorylation of mammalian rapamycin target proteins (mTOR) and P70S6 kinase (P70S6K) in the brain, and also enhanced the autophagy activation factor-Beclin 1 and microtube-associated protein light chain 3 II (LC3-II), thereby alleviating learning and memory impairment of SAMP8 mice. In addition, *Djulis* also increased autophagy, reduced

apoptosis and GPT level, and lessened fatty liver score. However, the related mechanism of *Djulis* on the aged sarcopenia is still unclear. Thus, the study aimed to investigate the effects of *Djulis* on muscle mass and muscle strength, and the possible protein synthesis and degradated pathways by aged sarcopenia animal model-SAMP8 mice. Three-month-old SAMP8 mice were divided into control, and different doses of *Djulis* groups, and fed for 12wks. Muscle strength was evaluated before sacrificed. After sacrificed, muscle tissue was separated and weighted. Muscle protein synthesis factor and muscle degradated factors were analyzed. The results shows that *Djulis* inhibited the autophagical activation factor-Beclin 1 by upregulating mTOR expression in muscle, decreasing LC3-II, thereby retarding muscle degradation, while the Sirt 1 also trend to be reduced. However, there was no significant difference between muscle synthesis signaling-including AKT and P70S6K among different groups. In conclusions, *Djulis* may improve muscle mass and muscle strength by enhancing the muscle degradated process to delaying the progression of sarcopenia caused by aging.

Keywords：sarcopenia, *Djulis*, muscle mass, muscle strength, protein synthesis, autophagy

TCVGH-PU1118103

運用深度學習技術應用於老人危險行為偵測

Using deep learning technology for dangerous behavior detection

張志宏/靜宜大學資訊傳播工程學系/副教授
洪哲倫/靜宜大學資訊傳播工程學系/教授
朱為民/臺中榮民總醫院急診部/主任
陳柏志/靜宜大學資訊管理學系碩士班/研究生

跌倒一直是老年人死亡的首要原因，因此跌倒自動檢測和識別技術對於即時偵測，發出警示是非常重要的急救要件之一。本計畫提出了一種有別於以往穿戴式感測器的方法，是基於圖像中人體相對位置的位移參數來識別跌倒行為是否發生。本計畫實現了一個基於 OpenPose 並結合具有時間序列深度學習神經網路模型 LSTM 進行影像識別，透過影像中人體跌倒的關節位移參數，並對識別出的參數進行簡單過濾，然後將過濾後的參數用於模型訓練，再將過濾後的參數用於模型的訓練，最後將模型部署到邊緣設備。實驗結果顯示本計畫所提出的方法能有效偵測跌倒發生。

Falls are consistently the top cause of death among seniors. At a time when the global population is getting older and fewer births. The shortage of nursing staff seriously affects the health care of the elderly. If information and communication technology can be used, automatic detection and identification the elderly fall, we believe it can reduce the injury of the elderly due to falls. This project proposed a method different from the previous wearable sensing device, which is based on the displacement of human relative positional parameters in the image to identify the occurrence of human fall. We implemented a system based on OpenPose and combined with the deep learning neural network model LSTM with time series, the image recognition is carried out, the human joint parameters of human posture falling and falling in the image are captured, and the identified parameters are simply filtered, and then the filtered parameters are used for model training then used the filtered parameters for model training, and finally deploy the model to the edge device. The experimental results show that the proposed method can significantly detect the falling.

TCVGH-PU1118104

探索潛力 TMPRSS2 抑制劑針對抗 covid-19

Exploring potential TMPRSS2 inhibitors for anti-covid-19

唐傳義/靜宜大學資訊工程學系/教授
陳春榮/臺中榮民總醫院研究部/研究員
鄭雅妮/臺中榮民總醫院研究部/研究助理
廖梓榕/臺中榮民總醫院研究部/研究助理
廖素蘭/臺中榮民總醫院研究部/副技師

在新藥開發上，電腦輔助藥物設計的角色，是針對某種疾病，設計出最有效藥物，並將盡可能的提高藥物的專一性，大幅降低藥物的副作用性，將活性化合物篩選及先導化合物優化的改進最為顯著，一直是藥物設計努力的方向。

SARS-CoV-2 利用病毒膜刺突蛋白(spike protein, S protein)進入宿主細胞，利用宿主細胞的 TMPRSS2 蛋白(Transmembrane protease, serine 2)對病毒自身的刺突蛋白進行切割與啟動膜融合動作，對於病毒的複製週期中發揮重要作用，因此在對抗 SARS-CoV-2 上 TMPRSS2 視為關鍵蛋白。

本計畫最主要的目的是要應用深度學習藥效基團平台，該平台將整合深度學習及藥效基團的兩大架構的技術於平台上，並融入新小分子結構比對技術以及藥物重組技術於所建立的平台上，運應本平台針對 TMPRSS2 進行新抑制劑篩選，可以進行多種電腦輔助藥物設計策略，進而測試及新抑制劑的研發設計。

在目前國際研究中 Camostat，Nafamostat，Leupeptin 藥物對於 TMPRSS2 有抑制效果，因此本計畫研究中，我們以 AI 建立了三老藥藥效基團團，以所需要的官能基基團建立篩選系統，運用系統篩選大型分子資料庫，找出針對 TMPRSS2 潛力化合物。並透過生物試驗進行驗證，確定我們所找出的潛力化合物具備比 Remdesivir 有夠佳優秀的抑制效果，在未來可以做進一步發展應用。

關鍵詞: 新冠病毒、跨膜絲胺酸蛋白酶 2、藥效基團、虛擬篩選、生物試驗

The core challenge of new drug design is to devise the most effective drugs of specific diseases, and to enhance the specificity of drugs in order to decreasing the side effect of drugs. In the modern age of drug design, CADD will play an indispensable role.

The coronavirus SARS-CoV-2 use spike protein (S protein) into the host cell, and use the TMPRSS2 protein of host cell to cleaving a spike protein and initiate membrane fusion. In the viral life cycle, TMPRSS2 as important role as a potential target to inhibit SARS-CoV-2.

The goal of this project is to use an integrated deep learning pharmacophore (DP-Pharma) platform. The techniques of deep learning and pharmacophore approaches will be integrated, and the new molecule structure comparison and molecule recombination schemes will also be implemented in this platform. Exploring potential TMPRSS2 inhibitors by the platform, some

drug design strategies can be performed and try to design new inhibitors for several applications.

In international research, Camostat, Nafamostat, and Leupeptin have been reported to stand for the inhibition of TMPRSS2 protein. In this proposal, we have build the pharmacophore model system of these three drugs and keep the necessary chemical features of a functional group. We have used the pharmacophore model system to screening the molecular database to discover potential inhibitors for the TMPRSS2 protein. By biological experiment, we confirm the potential compound X has better inhibitory effects than Remdesivir. Further, compound X has developed and applied.

Keywords: Coronavirus disease 2019, transmembrane serine protease 2, pharmacophore, virtual screening, biological experiment

榮聯計畫

TCVGH-NUU1118901

台灣藜對於經 IL-1β 刺激產生發炎症狀的軟骨細胞其功能性分析

Functionality of Chenopodium Formosanum on IL-1β Induced Inflammatory Chondrocyte

陳郁君/國立聯合大學化學工程學系/助理教授
陳志榮/臺中榮民總醫院病理檢驗部/主任
陳鈺萍/國立聯合大學化學工程學系

骨關節炎 (OA) 是常見的關節疾病之一，此外，這種慢性關節軟骨退行性疾病的患病率會隨著年齡的增長而逐漸增加。全世界 65 歲以上的老年人口中約有一半的人患有骨關節炎。骨關節炎的主要特徵包含了骨關節硬化、滑膜炎症和軟骨退化。促炎細胞因子和氧化壓力等多種因素被認為會導致骨關節炎的產生，進而影響軟骨基質的代謝，使得軟骨基質因受力產生破壞及損傷。而軟骨組織本身由於缺乏血管運送養分，使其自我修復能力受限。目前骨關節炎常見的臨床治療包括藥物治療、類固醇和玻尿酸注射，然而這些方法僅能緩解疼痛，不能有效地恢復軟骨基質。台灣藜是一種富含多酚和膳食纖維的穀類作物，文獻探討中發現台灣藜萃取物在治療大鼠結腸癌和皮膚細胞的修復具有抗炎、抗氧化及膠原蛋白相關的基因表現增加。因此本研究探討台灣藜萃取物對於以經 IL-1β 刺激 C20A4 軟骨細胞發炎之的功效性評估，實驗中先進行台灣藜萃取物的抗氧化能力分析，並利用基因表現分析添加台灣藜萃取物在發炎軟骨細胞上的抗發炎效果。從 WST-1 的結果顯示台灣藜對軟骨細胞沒有毒性，且若添加於經 IL-1β 刺激的軟骨細胞上，也不會影響其細胞活性。另外，從基因表現的數據上可發現添加 10 μg/ml 濃度的台灣藜萃取物在培養液當中，可有效降低發炎發炎的表達量，提升第二型膠原蛋白及其他細胞外基質合成相關基因。因此，未來應可搭載台灣藜萃取物在玻尿酸注射製劑當中，以做為骨關節炎早期預防或初期退化治療的製劑。

關鍵詞: 骨關節炎、軟骨、促炎細胞因子、台灣藜、基因表現分析

Osteoarthritis (OA) is one of the common joint diseases. In addition, the prevalence of this chronic articular cartilage degenerative disease gradually increases with age, and half of the world's elderly population over the age of 65 suffers from OA. The main features of OA are joint bone sclerosis, synovial inflammation and cartilage degeneration. Multiple factors, including pro-inflammatory cytokines and oxidative stress, are thought to contribute to the destruction and damage of OA cartilage. The self-repair ability of cartilage is limited. The current clinical treatment of OA includes drug therapy, steroids and hyaluronic acid injection. However, these methods can only relieve pain and cannot restore cartilage function. Djulis (Chenopodium Formosanum) is a cereal crop rich in polyphenols and dietary fiber. In the literature review, it was found that Djulis extract has anti-inflammatory, anti-oxidation and increased expression of collagen-related genes in the treatment of colon cancer and skin cell repair in rats. Therefore, this study explored the functional evaluation of the extract of Djulis on IL-1β induce inflammatory chondrocyte. The antioxidant capacity of Djulis was analyzed,

and the cytocompatibility and gene expression analysis were performed by adding IL-1β to induce cell inflammation. WST-1 results showed that Djulis possess no toxicity on C20A4 chondrocytes, and it will not affect the cell viability under IL-1β stimulation. Gene expression analysis results showed that the concentration of Djulis 10 μg/ml can reduce the expression of inflammatory related genes and enhance type II collagen and other genes related to extracellular matrix synthesis. suggesting that Djulis may be used in the treatment of OA in the future. According to aboved results, we suppose Djulis extract could be combined with hyaluronic acid injection as a therapy for early OA prevention or early OA stage treatment.

Keywords：Osteoarthritis, cartilage, pro-inflammatory cytokines, Djulis, gene expression analysis

TCVGH-NUU1118902

可採集下肢復健數位化資料之穿戴式裝置開發

Development of wearable devices collecting digital data for lower limb rehabilitation

吳有基/國立聯合大學電機工程學系/教授
韓欽銓/國立聯合大學資訊工程學系/教授
程遠揚/臺中榮民總醫院復健科/主任
黃鈺榮/國立聯合大學/博士生
江均賢/國立聯合大學/專任助理

復健訓練的過程常需消耗大量的醫療人力，且患者於復健過程當中，常無法依指定的醫囑重複執行出正確的動作，也無量化的客觀姿態數據指標來評估患者動作的品質及進步的狀況，其原因在於沒有適當便利穿戴的偵測設備，來進行復健資料的數位化。有鑒於此，本計畫基於先前的研究基礎，開發出一套可採集下肢復健數位化資料之穿戴式裝置，此裝置具有內含慣量量測單元之腰帶、膝帶、及腳踝帶，可採集復健動作姿態數據，以無線的方式傳輸至智慧型手機及雲端主機，並設計相關人工智慧演算法，建立姿態辨識模型，並於手機中執行復健姿態之即時辨識，以虛擬人型模型來重新呈現患者的復健動作，同時於手機上計算出復健量化數據，讓醫療人員有數據可以參考，評估患者復健成效，從而提高復健效果，邁向精準復健醫療。

It often takes a lot of medical manpower for therapists to execute rehabilitation programs on patients with lower limb disabilities. Patients may not be able to perform the correct movements repeatedly according to the specified medical orders during the rehabilitation training process when objective data collection of rehabilitation posture and quantitative indicators to evaluate the quality and progress of the patient's movements are not available. Therefore, the importance of appropriate wearable and convenient detection device to digitize rehabilitation data can never be overemphasized. In view of this, based on our previous research data, this project develops a wearable device that can collect movement data during lower limb rehabilitation, which include a waist belt, two knee belts, and two ankle belts using inertial measurement units (IMUs). These devices can collect rehabilitation posture data, and transmit data wirelessly to a smart phone and cloud host. An appropriate machine learning algorithm is designed to build a posture recognition model which is imported to the smart phone. The patient's rehabilitation posture is recognized in a real-time fashion and further presented by a virtual humanoid model (Unity). The quantitative rehabilitation data could also be calculated on the cell phone, so that healthcare providers can have the data to evaluate the effectiveness of patients' rehabilitation. The effectiveness of rehabilitation could thus be improved, and we can better achieve the concept of precision medicine in the field of rehabilitation.

TCVGH-NUU1118903

神經內分泌瘤Ki-67判讀模型之落地測試及修正

The developed AI model applied to estimate Ki-67 score for Neuroendocrine tumors: The bench to bedside testing

李佳燕/國立聯合大學電機系/教授
詹以吉/台中榮民總醫院病理檢驗部/主任
傅景佟/台中榮民總醫院病理檢驗部/主治醫師
陳律臻/台中榮民總醫院病理檢驗部/主治醫師
王慶萍/國立陽明交通大學電機系/學生
曾鈞銅/國立聯合大學電機系/學生

利用免疫組織染色法進行組織切片觀察已成為現今判讀腫瘤嚴重程度的檢查方式。然而，儀器成像的變異、觀察者染色的變異與組織型態多變使得專家在判讀大量切片上易面臨人工耗時與費力的問題，為此本計畫已於前期研究建立一套快速且準確的 Ki-67 病理切片自動判讀模型(KissNET)。由於 KissNET 模型使用台北榮總所提供的資料，因此為加強模型適用於不同場域、掃瞄儀器之影像，本計畫於台中榮總收集了 60 筆病患的 Ki-67 染色切片，並由醫師圈選出 114 個感興趣區域，執行 KissNET 模型的落地測試與應用。研究結果顯示，KissNET 判讀之修正率達 0.06，達到預期設定的小於一成，且藉由統計分析發現，KissNET 與醫師手動計數(manual counting)結果高度相關(r=0.977, kappa=0.892)，相關度優於 KissNET 與醫師肉眼(eyeballing)觀察(r=0.906, kappa=0.627)。最後，本計畫將 KissNET 模型設計出使用者界面，並已實際落地於臺中榮總病理部，提供病理科醫師可視化結果與相對應之 Ki-67 值。

Using immunochemical staining to observe tissue slices has become a standard method for determining the severity of tumor. However, the variations of imaging scanner, staining techniques, and morphological difficulties caused time-consuming and labor-intensive for experts to interpret large numbers of slices. To address this problem, we have developed a fast and accurate model (KissNET) in previous research for automatedly interpreting Ki-67 slices. This project collected 60 slices from patients at Taichung Veterans General Hospital and selected 114 regions of interest for interperation. The results showed that the revised rate was 0.06, which achieved the expected goal of less than 1%. Statistical analysis found that a high degree of correlation between the results of KissNET and patholosist's manual counting (r=0.977, kappa=0.892), which was higher than the correlation between KissNET and pathologist's eyeballing (r=0.906, kappa=0.627). Finally, a user interface was provided which was developed on KissNET model and successfully implemented in Taichung Veterans General Hospital, providing pathologists with visualized results and corresponding Ki-67 values.

TCVGH-NUU1118904

非侵葡萄糖濃度量測方法

Non-invasive glucose concentration measurement method

潘國興/國立聯合大學機械系/副教授
陳享民/臺中榮民總醫院醫學研究部/研究員
李書妤、Quoc-Thinh Dinh/國立聯合大學機械系/研究生

由於世界上糖尿病患者人數正在迅速增加，而傳統的血糖檢測方法對糖尿病患者來說既痛苦又昂貴。 本研究提出了一種基於微分穆勒矩陣系統圖形和多等離子體共振(SPR)的無創葡萄糖濃度測量方法。通過檢測 0~500 mg/dl 範圍內的水溶液葡萄糖濃度，證明了所提出技術的可行性。 結果表明，旋光角隨葡萄糖濃度呈線性變化。於 3 層石墨烯層 SPR 傳感器，所提出技術的分辨率高達 11.26 mg/dl。該系統為無創血糖測量應用提供了一種比傳統方法更有潛力、更舒適、更方便的技術。

Since the population of diabetics in the world is increasing rapidly and the traditional blood glucose detection method is painful and expensive for diabetes patients. This study proposes a non-invasive glucose concentration measurement based on the differential Muller matrix system and multiple-graphene-layer surface plasmon resonance (SPR). The feasibility of the proposed technique is demonstrated by detecting the glucose concentration of aqueous solution over the range of 0~500 mg/dl. The results show that the optical rotation angle varies linearly with the glucose concentrations over the considered range. The resolution of the proposed technique is as fine as 11.26 mg/dl for a 3-graphene-layer SPR sensor. This system provides a potential, comfortable, and more convenient technology than traditional methods for non-invasive blood glucose measurement applications.

TCVGH-NUU1118905

高靈敏度螢光病理診測技術之開發

Development of Highly Sensitive Fluorescent Pathological Diagnosis Technology

林永昇/國立聯合大學化學工程學系/教授
陳志榮/臺中榮民總醫院病理檢驗部/部主任
吳俊諺/國立聯合大學化學工程學系/大專生
吳致緯/國立聯合大學化學工程學系/大專生

在本研究中，我們先在體外找出最佳之間隔物長度，其中以 PEG6k 的 MEF 效果最佳，所以我們利用平均粒徑 4.80 ± 1.38 nm 之 Ag-PEG6k NPs 來當作細胞成像之 MEF 材料。在 Alexa Fluor 488 螢光染料對人類間質幹細胞的 β-actin 進行染色實驗中，螢光增強因子隨著 Ag-PEG6k NPs 濃度增加而增加，但隨著 Alexa Fluor 488 濃度的增加而減少，在濃度為 0.243 ppm 之 Ag-PEG6k NPs 與濃度為 0.625 ppm 之 Alexa Fluor 488 時，具有最佳的 MEF 效果，其增強因子可以高於 4。此外，Ag-PEG6k NPs 顯示出良好的生物相容性，未來 Ag-PEG6k NPs 可以應用於增強生物成像。

In this study, we first found out the optimal spacer length in vitro, and PEG6k had the best MEF. Therefore, Ag-PEG6k NPs with an average particle size of 4.80 ± 1.38 nm were used as the MEF material for cell imaging. In the experiment of Alexa Fluor 488 fluorescent dye staining β-actin of human mesenchymal stem cells, the fluorescence enhancement factor increased with the concentration of Ag-PEG6k NPs, but decreased with the Alexa Fluor 488 concentration. When Ag-PEG6k NPs at a concentration of 0.243 ppm and Alexa Fluor 488 at a concentration of 0.625 ppm, it had the best MEF effect, and its enhancement factor can be higher than 4. In addition, Ag-PEG6k NPs showed good biocompatibility, and Ag-PEG6k NPs can be applied to enhance biological imaging in the future.