112年度
臺中榮民總醫院暨中區大學及國立陽明交通大學
合作研究計畫成果

主辦單位：臺中榮民總醫院

協辦單位：國立中興大學、國立暨南國際大學、靜宜大學、中臺科技大學、逢甲大學、東海大學、國立臺中科技大學、弘光科技大學、大葉大學、國立聯合大學、國立陽明交通大學

Programs and Abstracts

112 年度臺中榮民總醫院暨中區大學及國立陽明交通大學合作研究計畫成果

主辦單位 臺中榮民總醫院

協辦單位 國立中興大學、國立暨南國際大學、
靜宜大學、中臺科技大學、逢甲大學、
東海大學、國立臺中科技大學、弘光科技大學、
大葉大學、國立聯合大學、國立陽明交通大學

112 年度
臺中榮民總醫院暨中區大學及國立陽明交通大學合作研究計畫成果發表會

主辦單位

臺中榮民總醫院

協辦單位

國立中興大學、國立暨南國際大學、靜宜大學、中臺科技大學、逢甲大學、東海大學、國立臺中科技大學、弘光科技大學、大葉大學、國立聯合大學、國立陽明交通大學

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	陳韻仔	楊嵐燕
	李佳霖	陳彥如	許碧紋			
國立中興大學	宋振銘（研發長）	侯明宏	林季千	張法正		
國立暨南國際大學	戴榮賦（研發長）	鄭玉玲				
靜宜大學	林智健（研發長）	王奕筑				
中臺科技大學	朱淑珍（研發長）	江青桂	林芷薾	黃莛瑜		
逢甲大學	陳錦毅（研發長）	林彩玉	嚴慧美			
東海大學	林惠真（研發長）	顧野松(副研發長)	李亞蒴			
國立臺中科技大學	陳夏蓮（研發長）	黃天麒(副研發長)	廖皎汝			
弘光科技大學	林聖敦（研發長）	莊正宏	李詠梅			
大葉大學	賴峯民（研發長）	蔡仁傑	鄭淑惠			
國立聯合大學	吳芳賓（研發長）	李芊慧				

臺中榮民總醫院暨中部地區大學合作研究計畫
成果發表會議程

08:30-09:00	報到&張貼海報				
09:00-09:10	長官致詞				
09:10-09:15	全體合照				
心血管代謝疾病與過敏免疫 (主持人：逢甲大學應用數學系/ 洪子倫特聘教授)		**計畫主持人**		**計畫共同主持人**	
		單位	**姓名**	**單位**	**姓名**
09:15-09:30	糖尿病臨床用藥下新穎基因 ca8 表達改變對葡萄糖代謝和重新吸收的影響	東海大學生科系	謝明麗	臺中榮民總醫院腎臟科	蔡尚峰
09:30-09:45	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(第二年)	臺中榮民總醫院藥學部	朱裕文	大葉大學藥用植物與食品保健學系	宋祖瑩
09:45-10:00	以術後大鼠模型研究普利斯德注射劑對心肌細胞的粒線體自噬影響	臺中榮民總醫院麻醉部	賴慧卿	東海大學生科系	趙偉廷
10:00-10:15	超高壓加工技術生產之米蛋白胜肽對改善糖尿病性心臟病機制之探討	靜宜大學食品營養學系	李柏憲	臺中榮民總醫院心臟內科	鄭諭聰
10:15-10:25	Q&A				
10:25-10:45	中場休息暨壁報評比				
精準醫學與其他前瞻創新研究 (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**
10:45-11:00	原兒茶醛藉由多元醇路徑抑制糖尿病腎病變引起的腎臟纖維化	臺中榮民總醫院腎臟科	鍾牧圻	弘光科技大學營養系暨營養醫學研究所	邱雅鈴
11:00-11:15	乳腺密度組織特徵識別：IVIM-MR 成像中使用深度神經網絡與信號強度衰減曲線進行分析。	國立中興大學電機工程學系所	歐陽彥杰	臺中榮民總醫院放射線部	陳詩華
11:15-11:30	運用頭戴顯示裝置改善病患與醫療人員之作業流程	臺中榮民總醫院放射腫瘤部	游惟強	東海大學工工系	王怡然
11:30-11:45	製備含微胞藥物之自修復抗菌水凝膠及其應用	國立中興大學化學工程學系所	黃智峯	臺中榮民總醫院心臟血管外科	王中琦
11:45-11:55	Q&A				
11:55-13:30	午餐				

癌症醫學 (主持人：國立聯合大學資訊管理學系/ 陳振東教授)		計畫主持人		計畫共同主持人	
		單位	姓名	單位	姓名
13:30-13:45	運用人類肺癌細胞及其抗化療細胞分析没食子酸月桂酯的抗肺癌機制	弘光科技大學 生物科技系(所)	程淑慧	臺中榮民總醫院 胸腔內科	楊宗穎
13:45-14:00	攝護腺癌 CT 灌注影像的最佳數據成像時間	臺中榮民總醫院 放射線部	劉明承	逢甲大學自動 控制工程學系	劉益瑞
14:00-14:15	利格列汀對於肝癌腫瘤的小鼠模式之影響	臺中榮民總醫院 內科部	吳明儒	國立中興大學 生物醫學研究所	張嘉哲
14:15-14:25	Q&A				
14:25-14:45	中場休息暨壁報評比				
人工智慧與智慧大數據醫療 (主持人：靜宜大學資訊工程學系/ 劉志俊主任)		計畫主持人		計畫共同主持人	
		單位	姓名	單位	姓名
14:45-15:00	以人工智能預測急診血行性感染病人臨床預後的表現	臺中榮民總醫院 急診部	胡松原	東海大學資管系/ 臺中榮民總醫院 急診部/ 臺中榮民總醫院 急診部	姜自強/ 馬建文/ 林帛震
15:00-15:15	人工智慧用於未閉導管的血流動力學之測試與驗證	逢甲大學精密系統設計學士學位學程	蔡鈺鼎	臺中榮民總醫院 兒童醫學中心	林明志
15:15-15:30	深度學習導引複雜型側流分析影像輔助判讀之研究-以雙通道糞便潛血之辨識為例	國立中興大學電機工程學系所	莊家峰	臺中榮民總醫院 胸腔內科	吳明峰
15:30-15:45	開發以慣量量測單元為主之中風後病患步態數據採擷分析系統	國立聯合大學 電機工程學系	吳有基	國立聯合大學 資訊工程學系/ 臺中榮民總醫院 復健醫學部/ 臺中榮民總醫院 醫學研究部	韓欽銓/ 程遠揚/ 陳享民
15:45-15:55	Q&A				
15:55-16:00	閉幕				

臺中榮民總醫院暨國立陽明交通大學合作研究計畫
成果發表會議程

08:30-09:00	報到				
09:00-09:10	長官致詞(第二會場)				
09:10-09:15	全體合照(第二會場)				
精準醫學與遺傳基因醫學 (主持人：國立中興大學分子生物學研究所/賴建成教授)		**計畫主持人**		**計畫共同主持人**	
		單位	**姓名**	**單位**	**姓名**
09:15-09:35	利用單細胞 RNA 定序及基因分型來研究急性骨髓細胞性白血病產生化學抗性之機制	臺中榮民總醫院血液腫瘤科	滕傑林	國立陽明交通大學生物藥學研究所	黃奇英
09:35-09:55	褪黑激素改善鏈脲佐菌素誘導的第一型糖尿病小鼠模型糖尿病視網膜病變經活化 PINK1 的線粒體自噬作用	臺中榮民總醫院醫學研究部	許美鈴	國立陽明交通大學傳統醫藥研究所	藍耿立
09:55-10:15	NOTCH3 R544C 基因變異者之功能性腦部 MRI 及腦白質病變相關因子研究	臺中榮民總醫院神經內科	李威儒	國立陽明交通大學生物科技學系	黃植懋
10:15-10:25	Q&A				
10:25-10:45	中場休息				
精準醫學與遺傳基因醫學 (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**
10:45-11:05	探討僵直性脊椎炎 HLA-B*27 以外之遺傳前置因子及風險評估	臺中榮民總醫院品質管理中心	陳信華	國立陽明交通大學生物科技學系	柯泰名
11:05-11:25	ABCG2 rs22311422 基因多態性、生活型態因子與腎結石之相關性研究	臺中榮民總醫院醫學研究部	林敬恒	國立陽明交通大學醫務管理研究所	林寬佳
11:25-11:45	HLA 基因及胺基酸變異與自體免疫疾病相關之探討	臺中榮民總醫院醫學研究部	陳一銘	國立陽明交通大學臨床醫學研究所	李美璇
11:45-11:55	Q&A				
11:55-13:00	午餐				
心血管代謝疾病與其他前瞻創新研究 (主持人：國立中興大學生命科學系/劉英明教授)		**計畫主持人**		**計畫共同主持人**	
		單位	**姓名**	**單位**	**姓名**
13:00-13:20	血栓病變動物模式保健功效探討	臺中榮民總醫院兒童醫學中心	王建得	國立陽明交通大學生物醫學資訊所	吳俊穎
13:20-13:40	探討 IL-4 的葡萄糖代謝異常改善作用特性	臺中榮民總醫院醫學研究部	陳春榮	國立陽明大學醫學生物技術暨檢驗學系	黃琤

13:40-14:00	主動式與被動式短波紅外高光譜成像儀於糖尿病周邊神經病變偵測輔助診斷比較之研究	臺中榮民總醫院醫學研究部	陳享民	臺中榮民總醫院新陳代謝科/臺中榮民總醫院眼科部/國立陽明交通大學生醫光電研究所	沈宜靜/周建志/陳奕帆
14:00-14:20	以磁振造影技術探究神經精神性狼瘡患者腦部膠淋巴系統功能	臺中榮民總醫院放射線部	蔡志文	國立陽明交通大學神經科學研究所/臺中榮民總醫院放射線部/臺中榮民總醫院放射線部	林慶波/陳文賢/陳虹潔
14:20-14:30	Q&A				
14:30-14:45	中場休息				
人工智慧與智慧大數據醫療 (主持人：國立中興大學化學工程學系/ 姜文軒副教授)		**計畫主持人**		**計畫共同主持人**	
		單位	**姓名**	**單位**	**姓名**
14:45-15:05	人工智慧準確判讀 ICG 影像定位淋巴管走向	臺中榮民總醫院重建整形外科	賴志昇	國立陽明交通大學資訊工程學系(所)	陳奕廷
15:05-15:25	建立主動脈瓣與胸主動脈的自動圈註量測深度學習模型	臺中榮民總醫院放射腫瘤部	游惟強	國立陽明交通大學生醫光電研究所	吳育德
15:25-15:45	使用深度學習在電腦斷層上勾畫海馬迴位置 – 立體空間影像配準與核磁共振資訊遷移	臺中榮民總醫院放射腫瘤部	黃靖文	國立陽明交通大學智慧系統與應用研究所	陳建志
15:45-15:55	Q&A				
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鍾牧圻 臺中榮民總醫院腎臟科/主治醫師
邱雅鈴 弘光科技大學營養系暨營養醫學研究所/教授
張譽騰 國立中興大學生物醫學研究所

TCVGH-HK1128002 **探討短鏈脂肪酸的免疫調節作用**

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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(所)/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

TCVGH-HK1128003 **以細菌內毒素誘導間質性膀胱炎的大鼠模式評估膀胱注射脂肪源血管基質組分幹細胞與單核球細胞的療效**

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林志學 弘光科技大學營養系暨營養醫學研究所/助理教授
蔡青倍 臺中榮民總醫院婦產部/主治醫師

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黃雅芳 弘光科技大學護理系(所)/助理教授
林志堅 臺中榮民總醫院精神部/主治醫師
張碧華 臺中榮民總醫院護理部/護理督導長
黃惠美 臺中榮民總醫院嘉義分院護理部/主任
吳佳娟 臺中榮民總醫院/研究助理

TCVGH-HK1128005 **建立紅斑狼瘡實驗動物模型並探討新穎小分子藥物治療紅斑狼瘡腎炎之療效**

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游勝傑 臺中榮民總醫院醫學研究部/契約副研究員
葉桂鶯 弘光科技大學物理治療系/副教授
周庭瑜 臺中榮民總醫院醫學研究部/研究助理

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林美伶 弘光科技大學護理系(所)/助理教授
張碧華 臺中榮民總醫院護理部/護理督導長
黃惠美 臺中榮民總醫院嘉義分院護理部/主任
吳郁嫻 弘光科技大學護理系/學生

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雷若莉 弘光科技大學護理系(所)/副教授
朱為民 臺中榮民總醫院家庭醫學部/科主任

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黃文男 臺中榮民總醫院過敏免疫風濕科/科主任
林屏沂 弘光科技大學護理系(所)/副教授

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程淑慧 弘光科技大學生物科技系(所)/副教授
楊宗穎 臺中榮民總醫院胸腔內科/主治醫師
許國堂 中山醫學大學醫學研究所/教授

TCVGH-HK1128010 **社區老年人接種 COVID-19 疫苗之經驗-質性研究**

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陳淑齡 弘光科技大學護理系(所)/教授
宋韋瑩 臺中榮民總醫院家庭醫學部/護理師
林冠品 弘光科技大學護理系(所)/助理教授
李沛憶 臺中榮總家庭醫學部/護理師
陳映羽 臺中榮總家庭醫學部/護理師

TCVGH-HK1128011 **口腔機能訓練對住院高齡病患之吞嚥功能及口腔健康生活品質之成效**

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陳曉容 弘光科技大學護理系(所)/助理教授
張彩秀 弘光科技大學護理系(所)/副教授
張碧華 臺中榮民總醫院護理部/督導長
葉雅慧 臺中榮民總醫院護理部/護理長

TCVGH-HK1128012 **下肢截肢病人復原力、社會支持與生活品質之縱貫性追蹤研究**

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張碧華 臺中榮民總醫院護理部/護理督導長
張家慧 弘光科技大學護理系(所)/助理教授
許海倫 臺中榮民總醫院護理部/護理師

榮東計畫

TCVGH-T1127801 **以人工智能預測急診血行性感染病人臨床預後的表現**

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胡松原 臺中榮民總醫院急診部/科主任
姜自強 東海大學資管系/副教授
馬建文 臺中榮民總醫院急診部/主治醫師
林帛震 臺中榮民總醫院急診部/主治醫師

TCVGH-T1127802 **長期使用抗生素對於焦慮行為之影響**

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顏怡君 東海大學生命科學系/助理教授
林志堅 臺中榮民總醫院精神部/科主任

TCVGH-T1127803 **使用生物製劑或 JAK 抑制劑治療之類風濕性關節炎患者罹患重大心血管事件及靜脈血栓的風險**

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陳信華 臺中榮民總醫院臨床資訊科/科主任
翁紹仁 東海大學工業工程與經營資訊學系/教授

TCVGH-T1127804 **牛樟芝萃取物對亨丁頓舞蹈症之保護作用及機轉探討-以 NLRP3 發炎體為標的**

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朱自淳 東海大學畜產系/副教授
陳呈旭 臺中榮民總醫院腎臟科/主任

TCVGH-T1127805 **糖尿病臨床用藥下新穎基因 ca8 表達改變對葡萄糖代謝和重新吸收的影響**

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謝明麗 東海大學生命科學系/教授
蔡尚峰 臺中榮民總醫院腎臟科/主治醫師
王寒冰 東海大學生命科學系/專題生
劉翔瑜 東海大學生命科學系/專題生
張君維 東海大學生命科學系/專題生
林彥昕 東海大學生命科學系/專題生
陳宣宇 東海大學生命科學系/專題生

TCVGH-T1127806 **3D列印客製化牙根柱設計製作與臨床驗證**

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葉家宏 東海大學工業工程與經營資訊學系/副教授
黃良吉 臺中榮民總醫院口腔醫學部/科主任
葉濬緁 東海大學工業工程與經營資訊學系/研究生

TCVGH-T1127807 **結合白斑症患部自動標記與處方資訊之治療評估系統**

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石志雄 東海大學資工系/副教授
翁毓菁 臺中榮民總醫院皮膚科/主治醫師
簡振宇 東海大學資工系/研究生

TCVGH-T1127808 **以術後大鼠模型研究普利斯德注射劑對心肌細胞的粒線體自噬影響**

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賴慧卿 臺中榮民總醫院麻醉部/科主任
趙偉廷 東海大學生科系/副教授

TCVGH-T1127809 **使用機器學習和大數據分析建立住院老年人出院後非預期性再住院與死亡預測模組**

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朱為民 臺中榮民總醫院家庭醫學部/科主任
楊朝棟 東海大學資工系/教授

TCVGH-T1127810 **運用頭戴顯示裝置改善病患與醫療人員之作業流程**

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游惟強 臺中榮民總醫院放射腫瘤部/主任
王怡然 東海大學工業工程與經營資訊學系/教授
翁紹仁 東海大學工業工程與經營資訊學系/教授
葉庭羽 東海大學工業工程與經營資訊學系/研究生
李翎瑜 東海大學工業工程與經營資訊學系/研究助理
張芮綺 東海大學工業工程與經營資訊學系/研究助理
阮氏楊 東海大學工業工程與經營資訊學系/研究助理
高莉淇 東海大學工業工程與經營資訊學系/研究助理

榮科計畫

TCVGH-NTCNC1128501 **探究組織架構與工作因子在不同部門護理人員的職場壓力與睡眠品質之影響-以某醫學中心為例**

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陳大仁	國立臺中科技大學資訊流通學院資訊管理系/教授
徐莞雲	臺中榮民總醫院護理部/護理長
葉月珍	國立臺中科技大學中護健康學院護理系/助理教授
李雅婷	國立臺中科技大學中護健康學院美容系/教授
林俊仰	國立臺中科技大學資訊流通學院資訊管理系
陳誠宗	國立臺中科技大學資訊流通學院資訊管理系
陳彥綸	國立臺中科技大學資訊流通學院資訊管理系
林揚凱	國立臺中科技大學資訊流通學院資訊管理系
邱語柔	國立臺中科技大學資訊流通學院資訊管理系
潘瑋琪	國立臺中科技大學資訊流通學院資訊管理系

榮逢計畫

TCVGH-FCU1128201 **製備奈米纖維複合安莫西林於藥物釋放及傷口敷料之應用**

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張育誠 逢甲大學材料科學與工程學系/特聘教授
周佳滿 臺中榮民總醫院外科部/主任
吳振宇 逢甲大學材料科學與工程學系/研究生
陳姿儒 逢甲大學材料科學與工程學系/專題生

TCVGH-FCU1128202 **人工智慧用於未閉導管的血流動力學之測試與驗證**

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蔡鈺鼎 逢甲大學精密系統設計學士學位學程/副教授
林明志 臺中榮民總醫院兒童醫學中心/主任

TCVGH-FCU1128203 **以透明質酸-靛氰綠-聚乳酸甘醇酸奈米螢光探針標定內皮淋巴細胞與建立淋巴水腫動物模型之研究**

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簡儀欣 逢甲大學材料科學與工程學系/副教授
賴志昇 臺中榮民總醫院重建整形外科/主治醫師
黃偉任 逢甲大學材料科學與工程學系/碩士班
蔡旻璇 逢甲大學材料科學與工程學系/大學部
林煒翔 逢甲大學材料科學與工程學系/大學部
高涵穎 逢甲大學材料科學與工程學系/大學部
馮金星 臺中榮民總醫院整形外科/醫事技術師

TCVGH-FCU1128204 **開發新穎多功能藥物釋放之雙層結構奈米纖維傷口敷料，其中外層為PU/PCL結合PVA含薑黃素和奈米抗發炎及抗菌功能之內層**

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駱榮富 逢甲大學材料科學與工程學系/教授
陳伊呈 臺中榮民總醫院重建整形外科/主任

TCVGH-FCU1128205 **攝護腺癌CT灌注影像的最佳數據成像時間**

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劉明承 臺中榮民總醫院放射線部/主治醫師
劉益瑞 逢甲大學自動控制工程學系/教授

榮葉計畫

TCVGH-DYU1128301 **蛹蟲草酒萃物抗過敏的療效評估-小鼠異位性皮膚炎模式**

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李美芳 臺中榮民總醫院醫學研究部/副研究員
吳建一 大葉大學藥用植物與食品保健學系/教授
朱裕文 臺中榮民總醫院藥學部/科主任

TCVGH-DYU1128302 **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(第二年)**

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朱裕文 臺中榮民總醫院藥學部/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 臺中榮民總醫院醫學研究部/副研究員

TCVGH-DYU1128303 **運動介入於乳癌存活者紫杉醇導致周邊神經病變之成效**

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王雅容 大葉大學護理系/副教授
洪志強 臺中榮民總醫院乳房腫瘤外科/主任
洪銘佳 臺中榮民總醫院乳房腫瘤外科/專科護理師
林佳嬅 臺中榮民總醫院乳房腫瘤外科/衛教護理師

榮暨計畫

TCVGH-NCNU1127901 **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中之胰島素及青春激素訊號影響雄性果蠅同性偏好的求偶行為**

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傅在峰	國立暨南大學應用化學系/教授
林志堅	臺中榮民總醫院精神部/主治醫師
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-NCNU1127902 **雷射法製作具有磁性及表面增強拉曼散射的奈米粒子來偵測循環腫瘤細胞**

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蕭桂森	國立暨南大學應用材料及光電工程學系/教授
周佳滿	臺中榮民總醫院兒童外科/主任
黃勝揚	臺中榮民總醫院兒童外科/主治醫師
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-NCNU1127903 **共同處理Regorafenib與蛋白酶體抑制劑引發肺癌細胞A549死亡的機制與應用**

P85

余長澤	國立暨南大學應用化系/副教授
楊宗穎	臺中榮民總醫院胸腔內科/科主任
陳若梅	國立暨南大學應用化系/博士後研究員
朱晨語	國立暨南大學應用化系/研究助理

榮臺計畫

TCVGH-CTUST1127701 **專一性預標靶免疫檢查點放射示蹤劑研製**

P87

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 臺中榮民總醫院核子醫學科/主任
龔瑞英 臺中榮民總醫院核子醫學科/醫事放射師

TCVGH-CTUST1127702 **奈米銀石墨烯複合基材應用於血管修復生物相容性之探討**

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楊孟寅 臺中榮民總醫院神經外科/主治醫師
劉百栓 中臺科技大學醫學影像暨放射科學系/教授

TCVGH-CTUST1127703 **以影像辨識為基礎的物件比對應用研究-以疏導門、急診滯留人員為例**

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林冠語 中臺科技大學護理系/副教授
蔡鴻文 臺中榮民總醫院醫務企管部/主任
林俊榮 國立勤益科技大學資訊工程系/助理教授

榮興計畫

TCVGH-NCHU1127601 **深度學習導引複雜型側流分析影像輔助判讀之研究-以雙通道糞便潛血之辨識為例**

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莊家峯	國立中興大學電機工程學系所/特聘教授
吳明峰	臺中榮民總醫院胸腔內科/醫事檢驗師
馬停偉	國立中興大學電機資訊學士班
許芷翎	國立中興大學電機所碩士班
羅迦勒	國立中興大學電機所碩士班

TCVGH-NCHU1127602 **植基於影像切割之深度學習模型及機器學習預測腦瘤患者之無進展生存期**

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鄭文郁	臺中榮民總醫院神經外科/主治醫師
蔡孟勳	國立中興大學資訊管理學系/教授
高浩章	國立中興大學資訊管理學系/研究生
白晏彰	國立中興大學資訊管理學系/研究生

TCVGH-NCHU1127603 **建立代謝流質譜追蹤平台研究模式探討捷抑炎療法對體內代謝動態平衡之影響**

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蔣恩沛	國立中興大學食品暨應用生物科技學系/終身特聘教授
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蘇雅麗	國立中興大學食生系/博士後研究員
陳怡婷	國立中興大學食生系/碩士生
黃薏安	國立中興大學食生系/碩專生

TCVGH-NCHU1127604 **研究使用 CD34 濃縮的週邊血球移植對神經壓傷的修復的效應**

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潘宏川	臺中榮民總醫院醫學研究部/科主任
蘇鴻麟	國立中興大學生命科學系/教授

TCVGH-NCHU1127605 **探討溶瘤家禽里奧病毒調控人外周血單核細胞及誘導胃癌細胞凋亡之分子機轉**

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

TCVGH-NCHU1127606 **皮膚代謝物在成人異位性皮膚炎致病機轉扮演的角色**

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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-NCHU1127607 **利格列汀對於肝癌腫瘤的小鼠模式之影響**

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吳明儒 臺中榮民總醫院內科部/部主任
張嘉哲 國立中興大學生物醫學研究所/教授
張譽騰 國立中興大學生物醫學研究所/博士後研究員

TCVGH-NCHU1127608 **硫酸軟骨素合成酵素在腫瘤微環境中對神經膠質瘤細胞增生與侵襲之研究**

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劉炯輝 國立中興大學醫學院學士後醫學系/副教授
楊孟寅 臺中榮民總醫院神經外科/科主任

TCVGH-NCHU1127609 **臨床前動物試驗-利用原位腦神經膠質瘤小鼠模型評估PEITC之功效與安全性**

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廖玟潔 國立中興大學醫學院學士後醫學系/教授
周育誠 臺中榮民總醫院神經外科/科主任
劉炯輝 國立中興大學組織工程與再生醫學博士學位學程/副教授

TCVGH-NCHU1127610 **玻尿酸嫁接非類固醇類藥製成生物可分解材料在術後傷口局部止痛與防沾粘之應用**

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莊敦堯 國立中興大學化學系所/副教授
呂俊德 臺中榮民總醫院重建整形外科/主治醫師

TCVGH-NCHU1127611 **探討imiquimod處理癌細胞後上調免疫檢查點配體HLA-G表達以削弱自然殺手細胞毒殺的機制**

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謝政哲 國立中興大學生物醫學研究所/教授
陳怡如 臺中榮民總醫院皮膚科/主任
李政宜 國立中興大學生物醫學研究所/博士候選人
張茂嘉 國立中興大學生物醫學研究所/碩士班研究生

TCVGH-NCHU1127612 **糖尿病動物衰弱表現型與因子探討**

P112

林時逸 臺中榮民總醫院高齡醫學中心/主治醫師
陳文英 國立中興大學獸醫學系所/教授

TCVGH-NCHU1127613 **褪黑激素改善db/db mice第二型糖尿病小鼠模型糖尿病視網膜病變經活化PINK1線粒體自噬作用**

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許美鈴 國立中興大學生物醫學研究所/教授
王俊興 臺中榮民總醫院新陳代謝科/主治醫師
李芸萱 國立中興大學生物醫學研究所/助理

TCVGH-NCHU1127614 **PAX3在台灣膠質瘤細胞複製壓力誘導的cGAS-STING途徑活化和抗藥中的關係探討**

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成果報告摘要

榮弘計畫

TCVGH-HK1128001

原兒茶醛藉由多元醇路徑抑制糖尿病腎病變引起的腎臟纖維化

Protocatechuic aldehyde inhibits diabetic nephropathy-induced renal fibrosis through the polyol pathway

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計畫目標：深入探討原兒茶醛抑制糖尿病腎病變所引起的腎臟纖維化之機制

計畫背景及目的：糖尿病為一種代謝疾病，特徵是血糖長期高於標準值。糖尿病腎病變為造成末期腎病變的主要途徑，糖尿病腎病變通常在糖尿病發生後十五至二十年開始有臨床變化，而且幾乎全會發展成末期腎病變，末期時通常會導致腎臟纖維化，最後發展為末期腎臟病。糖尿病腎病變的會出現腎絲球肥大、基底膜增厚、系膜擴張及葡萄糖與脂質代謝異常。原兒茶醛為一種天然水溶性多酚化合物，來源於丹參與大麥茶，同時為多元醇路徑中限制速率的酵素醛糖還原酶的抑制劑。原兒茶醛具有廣泛的藥理作用，包括抗氧化、抗纖維化、抗血栓形成和抑制發炎等特性。先前已有研究證實原兒茶醛能減輕肺臟纖維化及肝臟纖維化。在先前動物實驗結果中，我們發現原兒茶醛能有效降低二型糖尿病老鼠所引起的腎功能衰退、腎絲球肥大、腎臟纖維化、氧化與發炎反應等，但其中的機轉尚待釐清。我們推測可能與多元醇路徑及醛糖還原酶有關。本計畫旨在利用細胞實驗深入探討原兒茶醛減緩糖尿病腎病變所引起的腎臟纖維化之機轉。

研究方法：首先，利用大鼠腎臟纖維母細胞在高糖環境中分析原兒茶醛對於多元醇路徑中醛糖還原酶及山梨醇脫氫酶的表現量與活性,同時還會檢測多元醇路徑的醣類。其次，將檢視原兒茶醛使用能否改變山梨醇堆積後所造成的氧化壓力和乙型轉化生長因子訊號路徑。再者，為了驗證多元醇路徑及醛糖還原酶的角色，利用過表達或是敲低醛糖還原酶的方式去評估原兒茶醛的抑制效果是否透過多元醇路徑。最後，我們將分析山梨醇脫氫酶的表達是否有幫助減少山梨醇的堆積以達到抑制纖維化的效果。

預期研究成果：先期研究結果證明在動物實驗中原兒茶醛會抑制糖尿病所引起腎臟纖維化、氧化壓力、腎功能，以及醛糖還原酶蛋白量。因此我們想透過細胞實驗共同驗證是否與動物實驗結果同樣具有不錯的療效並更進一步探索其中機轉。這項研究成果將鼓勵糖尿病患者更積極使用醛糖還原酶抑制劑，達到腎臟纖維化的效果。我們將整合實驗結果並發表在優質期刊中。

Study objective: To clarify the mechanism of protocatechuic aldehyde inhibiting renal fibrosis induced by diabetic nephropathy.

Study background and rationale: Diabetes is a metabolic disease characterized by a long-term rise in blood glucose above the standard value. In many countries, diabetic

nephropathy (DN) is the primary cause of end-stage nephropathy. Approximately 20% to 40% of diabetic patients will have DN. These include the development of end-stage nephropathy, which usually leads to renal fibrosis and ultimately end-stage renal disease (ESRD). Protocatechuic aldehyde (PCA) is a natural water-soluble polyphenolic compound derived from Salvia miltiorrhiza. Previous studies have indicated that PCA has a wide range of pharmacological effects, including anti-oxidation, anti-fibrosis, anti-thrombosis, and inhibition of inflammation. Our team has found in animal studies that PCA can effectively reduce renal fibrosis in mice with type 2 diabetes, but the mechanism remains to be clarified, we predict these might correlate to polyol pathway and AR. The purpose of this project is to further explore the mechanism of PCA in reducing renal fibrosis induced by DN.

Study method: First, we set up rat kidney fibroblast cell line NRK-49F as the cellular model and then analyze the expression and enzymatic activity of AR and sorbitol dehydrogenase (SDH) in a high-glucose environment after PCA treatment. Secondly, the accumulation of sorbitol will lead to oxidative stress and transforming growth factor- β (TGF- β) signaling pathways. Thirdly, in order to verify the role of the AR, the overexpression or knockdown of AR will be used to evaluate whether the inhibitory effect of PCA is through the AR and the polyol pathway. Finally, we will analyze whether the expression of SDH reduces the accumulation of sorbitol to achieve the effect of inhibiting fibrosis.

Expected study results: The preliminary results proved that PCA inhibits diabetes-induced renal fibrosis, oxidative stress, renal function indicators, and AR protein expression in animal studies. Therefore, we would like to verify whether it has the similar curative effect as the results of animal experiments through cell experiments and further explore the mechanism. The results of this research will encourage more active use of ARIs in diabetic patients to achieve the effect of renal fibrosis. We will integrate experimental results and publish them in premium journals.

TCVGH-HK1128002

探討短鏈脂肪酸的免疫調節作用

Effects of short chain fatty acids on immune regulation

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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。本實驗係透過RAW264.7巨噬細胞株模式，持續探討短鏈脂肪酸的抗發炎活性。LPS刺激會增加M1型巨噬細胞促發炎分子表現釋出，包括TNF-α、IL-1β、NO。Sodium Butyrate及Sodium Propionate，都可降低LPS活化的表現釋出。同一條件下，LPS會增加IL-4、IL-10表現釋出。Sodium Butyrate及Sodium Propionate本身都可促進IL-4及IL-10表現釋出。與LPS共同處理時，IL-4及IL-10釋出變化，卻沒有發現加乘效應。LPS刺激會增加M1型巨噬細胞及促發炎相關分子表現，包括Drp1 S616磷酸化、ERK磷酸化、AMPK磷酸化、IRF5、IRF8、P2X4R、P2X7R、H3K9甲基化、H3K9乙醯化；降低M2型巨噬細胞及抑發炎相關分子表現，包括CD163、Arginase 1、CD206。Sodium Butyrate及Sodium Propionate，可降低LPS造成的Drp1 S616磷酸化、ERK磷酸化、AMPK磷酸化、IRF5、IRF8、P2X4R、P2X7R表現。對於CD163、Arginase 1表現低下的逆轉活性，卻不明顯。CD206的低下，卻可以稍微改善。增加LPS誘發的H3K9甲基化幅度。雖然本身顯著提升H3K9乙醯化，加乘性不明顯。H3K27乙醯化方面，與H3K9乙醯化變化相近。但是對於Sirt1及EZH2方面，各處理組間沒有顯著差異。以JC-1量測粒線體膜電位變化。LPS刺激RAW264.7細胞，降低粒線體膜電位，造成粒線體異常。Sodium Butyrate及Sodium Propionate都可緩解變化。以MitoTracker進一步量測粒線體變化。LPS刺激RAW264.7細胞，降低粒線體完整性，造成粒線體異常。Sodium Butyrate及Sodium Propionate都可緩解變化。雖然本計畫有新發現，但是詳細的分子作用機制，仍需持續深入探討。

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. Using RAW264.7 macrophage cell model, this study aimed to further investigate the anti-inflammatory actions of short chain fatty acids. LPS increased expression of markers related to macrophage M1 polarization and pro-inflammatory cytokine expression, including TNF-α, IL-1β, NO. Sodium Butyrate and Sodium Propionate all alleviated the expression of those molecules. At the same condition, LPS stimulation increased expression of IL-4 and IL-10. Although Sodium Butyrate and Sodium Propionate alone had potential to cause expression of IL-4 and IL-10, they had little effect on expression in LPS-stimulated cells. LPS stimulation increased expression of P-Drp1 S616, P-ERK, P-AMPK, P2X7R, P2X4R, IRF5, IRF8, H3K9me2, H3K9ac and decreased expression of CD206, Arginase 1, CD206. Sodium Butyrate and Sodium Propionate had alleviative effects on P-Drp1 S616, P-ERK, P-AMPK, P2X7R, P2X4R, IRF5, IRF8, whereas had little effet on CD163 and Arginase 1. However, Sodium Butyrate and Sodium Propionate attenuated CD206 redution and increased H3K9me2. Sodium Butyrate and Sodium Propionate slightly increased H3K9a and H3K27ac and failed to cause further increase in LPS-stimulated ells. Regarding Sirt1 and EZH2, there was no significant difference among groups. LPS stimulation disrupted mitochondrial membrane potential and integrity, as evidenced by JC-1 staining and MitoTracker staining and the disruption was attenuated by Sodium Butyrate and Sodium Propionate. 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.

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以細菌內毒素誘導間質性膀胱炎的大鼠模式評估膀胱注射脂肪源血管基質組分幹細胞與單核球細胞的療效

Evaluate the therapeutic effect of adipose-derived stromal vascular fraction cells and monocytes on interstitial cystitis/ bladder pain syndrome by a lipopolysaccharide induced rat model

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間質性膀胱炎/膀胱疼痛症候群是膀胱黏膜下層及肌肉層的慢性發炎疾病，目前仍無有效的治療方法。前人的研究發現脂肪源血管基質組分細胞與單核球細胞都具有抗發炎的效果，但是，仍缺乏足夠的證據支持使用這兩種細胞治療間質性膀胱炎。此外，至今仍無確立的動物實驗模式可用於間質性膀胱炎的療效評估或病理分析。因此，我們嘗試在本計畫依序進行兩部分研究工作：一是以細菌內毒素誘導方式建立間質性膀胱炎大鼠模式，二是在建立實驗模式的大鼠膀胱壁注射治療用細胞評估療效。我們將10 週齡的雌性Sprague-Dawley大白鼠，以每週1次、連續進行5週的方式，在膀胱內灌注細菌內毒素溶液，誘發間質性膀胱炎，然後從同品系大鼠的脂肪組織分離脂肪源血管基質組分細胞，以及從血液分離單核球細胞，將取得的細胞注射在大暑膀胱壁上評估對間質性膀胱炎的療效。注射細胞後第七天，犧牲大鼠，取下膀胱，進行膀胱組織學染色(H&E, Masson’s trichrome)。由病理切片發現，細菌內毒素的誘導模式可以在膀胱壁造成發炎細胞聚集與纖維化病變，膀胱壁注射單核球細胞雖可減輕纖維化病變，但是卻沒有顯著減少發炎細胞的浸潤，注射脂肪源血管基質組分細胞甚至有更嚴重的發炎現象，我們的結果顯示,細菌內毒素誘導模式似乎可行,但是需要再調整誘導方式與使用動物的品系，治療用細胞在注射前的處理也需要再調整。

關鍵詞：間質性膀胱炎/膀胱疼痛症候群，脂肪源血管基質組分細胞、單核球細胞、膀胱注射治療，間質性膀胱炎大鼠模式

Interstitial cystitis/bladder pain syndrome (IC/BPS) is chronic inflammation disorder mainly within the submucosal and muscular layers of the bladder. There is lack of effective therapy for IC/PBS, and no generally accepted animal model for evaluation. Previous studies reveal the anti-inflammatory effects of adipose-derived stromal vascular fraction cells (ADSVFs) and monocytes. Therefore, in this study, we intend to set a IC/BPS rat model up, and, to evaluate the efficacy of ADSVFs and monocyte in vivo. Female Sprague-Dawley (SD) rats in 10 weeks old were instilled lipopolysaccharide intravesically once per week for consecutive 5 weeks followed by injection of ADSVFs or monocyte into their bladder wall. After 7 days of cell injection, rats were sacrificed, their bladders were harvested en bloc, immersed into 10% buffered formalin. A 3~5mm paraffin sections were cut and staining with

hematoxylin and eosin (H&E) stain and Masson's trichrome stain. Histological studies shown the inflammatory cell infiltration and collagen formation in each animal's bladder wall. However, higher score of inflammation in ADSVFs and monocyte treated animals than sham treatment rats indicate the adverse effect of cells treatment, despite the slightly lower inflammatory sign in monocyte treated rats. Our result suggests the possibility of LPS induction for IC/BPS model setup, but the protocol should be refinement, include the using animal strain and experimental time-line. The pre-treatment of therapeutic cells also should be concerned.

Keywords：interstitial cystitis, adipose-derived stromal vascular fraction cells, monocytes

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探討數位媒體教材對ADHD兒童主要照顧者照護壓力相關症狀之成效

To investigate the effectiveness of parenting stress in ADHD children's caregiver in using digital media

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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兒童之主要照顧者的照護壓力與神經傳導物質有關，尤其是Cortisol、Serotonin、Melatonin、IL-6、IL-10等生理指標。
研究目的：探討數位媒體教材介入對ADHD主要照顧者之降低照護壓力及憂鬱症狀、提升睡眠及生活品質之成效及對減輕ADHD兒童症狀之成效。
研究方法：本研究設計採隨機試驗研究設計，以電腦使用隨機取樣方式來進行簡單抽樣取樣分成實驗組和對照組各30人。實驗組為接受數位媒體教材方案的ADHD兒童之主要照顧者，對照組則提供一般衛教照護，活動介入成效將於介入前、介入後、介入後一個月、三個月和六個月評估主要照顧者照護壓力相關症狀成效指標。
預期成效：數位媒體教材介入對ADHD主要照顧者之降低照護壓力及憂鬱症狀、提升睡眠及生活品質之成效及對減輕ADHD兒童症狀有成效。

Background：Attention deficit/hyperactivity disorder (ADHD) is one of the most common mental developmental disorders in pediatric mental health clinics, with symptoms including inattention, hyperactivity, and impulsivity. Studies have found that the care stress of the primary caregivers of ADHD children is related to neurotransmitters, such as Cortisol, Serotonin, Melatonin, IL-6, and IL-10.
Research Purpose：To investigate the effectiveness of digital media teaching material intervention on reducing care stress and depressive symptoms, improving sleep and quality of life among primary caregivers of ADHD children, and reducing the symptoms of ADHD children.
Research Method：The design of this study adopts a randomized control trial design, using random sampling to conduct simple sampling and dividing into the experimental group and the control group. The experimental group was the primary caregivers of ADHD children who received the digital media teaching material program, while the control group provided general health education care. Outcome measurement are caregiver stress-related symptoms.
Anticipate Outcomes：The digital media teaching material intervention will be effective in reducing care stress and depressive symptoms, improving sleep and quality of life for primary caregivers of ADHD children, and reducing symptoms in children with ADHD.

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建立紅斑狼瘡實驗動物模型並探討新穎小分子藥物治療紅斑狼瘡腎炎之療效

Establishing an experimental animal model of systemic lupus erythematosus and evaluating the efficacy of novel small molecule compound in the treatment of lupus erythematosus nephritis

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紅斑狼瘡為一種自體免疫疾病，患者的免疫系統會過度的活化並產生全身性發炎、自體抗體以及腎臟衰竭等症狀。在台灣，紅斑狼瘡的盛行率為37.0~97.5/每十萬人，其中女性的患病比率遠大於男性。除此之外，紅斑狼瘡的共病包括了黃斑部病變，心血管疾病，代謝症候群、骨關節病變等等。目前治療紅斑狼瘡的方式為抗瘧疾藥物、免疫抑制劑、輔助化療以及生物製劑。然而，這些藥物的使用在臨床上仍有未被滿足的地方，例如：使用免疫抑制劑所造成的嚴重副作用以及無法以單一機轉的藥物治療所有不同型態的紅斑狼瘡患者。新藥開發應用於治療紅斑狼瘡的動物模型主要以化學物質誘導產生紅斑狼瘡症狀的方式為主。本研究計劃的主旨為建立本院紅斑狼瘡動物模型並於日後應用於評估新穎小分子藥物的療效。我們使用不同濃度的咪喹莫特塗抹於小鼠耳朵12週來誘導小鼠產生紅斑狼瘡的症狀，血清中的自體抗體濃度、尿液中的肌酸酐濃度以酵素結合免疫吸附分析法測量。脾臟中的T細胞與B細胞分布以流式細胞儀測量。腎臟的病變已病理組織切片分析。結果顯示，經過10 mg咪喹莫特塗抹於小鼠耳朵12週之後可以誘導小鼠產生anti-Sm以及anti-dsDNA自體抗體，脾臟中Th17、 Th1以及age related B細胞的表現增加，腎絲球損傷以及免疫細胞浸潤增加。透過本研究，我們成功的建立紅斑狼瘡的小鼠模型，於日後可以進一步應用於分析新穎藥物的效果。

Systemic lupus erythematosus (SLE) is an autoimmune disease in which the patient's immune system is overactivated and produces symptoms such as systemic inflammation, autoantibodies, and kidney failure. In Taiwan, the prevalence of SLE is 37.0-97.5 per 100,000 people, with the prevalence in women being much higher than that men. In addition, the comorbidities of SLE include macular degeneration, cardiovascular disease, metabolic syndrome, bone and joint disease, etc. Current treatments for SLE include antimalarial drugs, immunosuppressants, adjuvant chemotherapy, and biologics. However, the use of these drugs still has unmet clinical needs, such as the severe side effects caused by the use of immunosuppressants and the inability to treat all patients with different SLE types with a single drug. The animal models used in the development of new drugs to treat SLE mainly use chemical substances to induce the symptoms of SLE. The purpose of this research project is to establish an animal model of SLE in our hospital and apply it to evaluate the efficacy of novel small molecule drugs in the future. We applied imiquimod (IMQ) at different concentrations

on mice ear for 12 weeks to induce symptoms of SLE. The concentration of autoantibodies in the serum and the concentration of creatinine in the urine were measured by ELISA. The expression of T cells and B cells in the spleen was measured by flow cytometry. The kidney pathology was analyzed by H&E stain and PAS stain. The results show that 10 mg of IMQ applied on mice year for 12 weeks can induce the production of anti-Sm and anti-dsDNA autoantibodies in mice serum, increase the expression of Th17, Th1 and age-related B cells in the spleen, and increase renal inflammation and immune cell infiltration in the kidney. Through this study, we successfully established a mouse model of SLE, which can be further used to analyze the effects of novel drugs in the future.

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影響女性輪班護理師疲勞之相關因素與發炎指標之研究

Influence of fatigue and inflammation markers in shift work nurses

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護理師是醫院中最重要的24小時照顧病患的專業人員，輪班是不可避免的工作部分。本研究的目的是調查大夜班女性護理師的疲勞及其相關因素。研究採用橫斷式相關性研究設計，方便取樣，自2023年5月至10月在台灣中部某醫學中心進行，研究對象為大夜班護理師，總計227位參與。研究發現，夜班女性護理師中有84%呈現疲勞現象，且有67.6%的護理師受到睡眠干擾的問題。在研究中發現，護理師在經前3天至經期4天期間，疲勞程度有統計上的差異。然而，疲勞與年齡、單位、工作經驗、cortisol、IL-6、IL-1β等發炎指標之間並無統計上的差異。日夜作息習慣和健康促進生活型態對疲勞並未產生影響，但自我效能與疲勞呈現負相關。此外，疲勞與睡眠干擾、知覺壓力、事件衝擊、憂鬱呈現正相關。夜班護理師在下班後感到最明顯的睏倦，其次為5-6點之間。本研究提供了解夜班護理師疲勞狀況的前景資料，未來研究應重點關注如何協助護理師處理與疲勞相關的生理和心理問題。

關鍵詞：護理師、輪班、疲勞

Nurses are the essential professionals in hospitals, providing 24-hour care to patients, and shift work is an inevitable aspect of their job. The purpose of this study is to investigate fatigue and its related factors among female nurses working the night shift. Employing a cross-sectional correlational research design and convenient sampling, the study was conducted from May to October 2023 at a medical center in central Taiwan, with a total of 227 night shift nurses participating. The study found that 84% of female night shift nurses experienced fatigue, and 67.6% reported issues with sleep disturbance. Significant differences in fatigue levels were observed during the 3 days before menstruation to 4 days into the menstrual period. However, there were no statistically significant differences in fatigue concerning age, unit, work experience, cortisol, IL-6, IL-1β, and other inflammatory indicators. Daily sleep-wake habits and health-promoting lifestyles did not impact fatigue, but self-efficacy showed a negative correlation with fatigue. Additionally, fatigue was positively correlated with sleep disturbance, perceived stress, event impact, and depression. Night shift nurses reported the most noticeable fatigue after finishing their shift, followed by the period between 5-6 am. This study provides valuable insights into the fatigue status of night shift nurses, emphasizing the need for future research to focus on addressing the physiological and psychological issues related to fatigue and supporting nurses in managing these challenges.

Keywords：Nurses, shift work, fatigue

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探討老年死亡病患接受安寧緩和療護與身體約束及積極性治療之相關:回溯性次級資料分析研究

To explore the relationship of physical restraint and curative treatment of elderly deceased patients during palliative care: a retrospective secondary data analysis study

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背景：對接近生命盡頭的長者使用身體束縛可能會增加痛苦和喪失尊嚴。關於長者生命最後階段在醫院環境中影響使用約束的頻率和因素的資訊相當有限。本研究的目的在確定住院長者使用身體約束的發生率和預測因子;2.探討臺灣緩和治療病房的老年科醫生和內科醫生在處方行為及治療選擇方面的差異。

方法：本研究運用回溯性次級資料分析法，針對中部某教學醫院之病例進行研究，包括2019年1月至2023年9月期間入住緩和治療病房的所有癌症患者。排除數據不足之個案後已進行分析。身體約束被定義為在住院期間受到身體約束超過8小時並接受醫療指令。我們回顧性地從測量的變數中確定了使用約束的潛在危險因素，包括初步診斷的類型、藥物則包括苯二氮平類 (BZD) 和強阿片類藥物、鼻胃管、擬音插入、出院原因和醫生的專業。6名醫生包括1名老年病醫生和5名內科醫生。包括苯二氮平類 (BZD)藥物使用和強阿片類藥物使用在內的處方行為被收集在本研究中。研究還記錄了幾種治療和檢查，例如鼻胃管、Foley 插入、中心靜脈導管插入、X 射線的使用和計算機斷層掃描（CT）的使用。採用多因素logistic回歸分析預測軀體約束的危險因素及分析老年病醫生和內科醫生的處方行為和治療選擇的差異。

研究結果:本研究結果收集2019—2023年共納入688例患者,平均年齡為82.1歲(SD 13.1)。69%的參與者是男性。在調整多個影響因素後發現，使用苯二氮平類 (BZD)（OR：2.39 95% CI：1.40-4.08）和鼻胃管（OR：2.57 95% CI：1.48-4.47）是預測身體約束的重要危險因素。次級分析顯示,除了使用苯二氮平類 (BZD)藥物和鼻胃管外,女性癌症患者(OR: 2.57,95% CI：1.48-4.47）也是一個顯著的危險因子。在6名醫生包括1名老年病醫生和5名內科醫生中，452例患者（65.7%）接受老年病診科護理。在調整了多種因素后，與住院醫生相比，老年病醫生使用強阿片類藥物較少（OR：0.67,95% CI：0.46-0.97），CT 使用較少（OR：0.37,95% CI：0.19-0.71）。苯二氮平類 (BZD)的處方顯示老年病醫生和實習醫生之間沒有差異。亞組分析顯示，男性（OR：0.49,95% CI：0.31-0.79）和 65 歲以上患者（OR：0.65,95% CI：0.45-0.95）在老年病醫生的護理下，阿片類藥物處方的強度較低。

結論與應用：這是第一個探索亞洲預測身體約束的風險因素的研究，也是第一個探討緩和治療病房老年病醫生和內科醫生之間處方行為和治療選擇差異的研究。緩和治療專業人員應注意在住院的絕症患者中使用苯二氮平類 (BZD)和鼻胃管，建議未來仍應持續進行研究，以確定不同專業的緩和治療醫生的適當教育計劃。

關鍵詞：老年死亡病患、安寧緩和療護、身體約束、積極性治療、回溯性次級資料分析

Backgrounds：The utilization of physical restraints in patients approaching the end of life can potentially contribute to increased distress and a loss of dignity. Limited information exists regarding the frequency and factors that influence the application of restraints in hospital settings during the terminal phase of a patient's life. The aim of this study was to 1.ascertain the occurrence and factors that forecast the utilization of physical restraints in hospitalized adults;2.explore the differences of prescribing behavior and treatment choices between geriatrician and internist in palliative care unit in Taiwan.

Methods：Data was collected from a single regional hospital in central Taiwan. All terminally ill patients admitted to palliative care unit from January 2019 to September 2023 were included. We excluded those who had missing data. Physical restraint was defined as being physically restrained during hospitalization for more than 8 hours and with medical order. We retrospectively identified potential risk factors for restraint use from among the variables measured, including type of primary diagnosis, medications including benzodiazepine (BZD) and strong opioid administered, nasogastric tube, foley insertion, reason of discharge, and specialty of physician. Multivariate logistic regression was used to analyze the risk factors predicting physical restraint. 6 physicians were the primary care doctors for those patients, including one geriatrician and 5 internists. Prescribing behaviors including benzodiazepine (BZD) use and strong opioid use were documented. Several treatments and examinations such as nasogastric tube, foley insertion, central venous catheter insertion, use of X-ray and use of computed tomography(CT) were also recorded. Multivariate logistic regression was used to analyze the differences of prescribing behavior and treatment choice between geriatrician and internist.

Results：From 2019 to 2023, 688 patients with average age of 82.1 (SD 13.1) were included in final analysis. 69% of all participants were male. After adjusting multiple confounding factors, use of BZD (OR: 2.39 95% CI: 1.40-4.08), and nasogastric tube (OR: 2.57 95% CI: 1.48-4.47) were significant risk factor predicting physical restraint. Subgroup analysis showed that female with cancer (OR: 2.57 95% CI: 1.48-4.47) was also one significant risk factor, besides use of BZD and nasogastric tube. 452 patient (65.7%) were cared by geriatrician. After adjusting multiple confounding factors, compared with internists, geriatrician had lesser use of strong opioid (OR: 0.67 95% CI: 0.46-0.97), and lesser use of CT (OR: 0.37 95% CI: 0.19-0.71). The prescription of BZD showed no differences between geriatrician and internist. Subgroup analysis showed that male (OR: 0.49 95% CI: 0.31-0.79) and patients more than 65 years old (OR: 0.65 95% CI: 0.45-0.95) had lesser strong opioid prescription when cared by geriatrician.

Conclusions：To the best of our knowledge, this is the first study exploring risk factors predicting physical restraint in Asia and exploring differences of prescribing behavior and treatment choice between geriatrician and internist in palliative care unit. Future research is warranted to identify proper educational program for palliative care physician with different specialty.

Keywords：elderly deceased patients, palliative care, physical restraint, curative treatment, retrospective secondary data analysis

TCVGH-HK1128008

自體免疫性疾病患者的嚴重感染之跨國比較研究

Severe infection in patients with autoimmune diseases: A Cross-national comparative study

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引言：嚴重感染是自體免疫病患者的一個重要問題。我們試圖估計在台灣和美國，選擇性自體免疫病患者相對於一般人口的嚴重感染率

方法：這是一項回顧性的世代研究，利用2000年至2013年間的住院保險資料庫資料，估計了在特定環境下，患有全身性紅斑狼瘡（包括腎外紅斑狼瘡和紅斑腎炎）、類風濕性關節炎和原發性膜性腎病的患者與一般人口相比的標準化嚴重感染發生率和比率。使用多變量的Cox比例風險模型來估計嚴重感染的調整風險比，並根據年齡、性別、索引年、先前的嚴重感染、合併症和藥物進行調整。

結果：在台灣，一般人口和患有原發性膜性腎病、類風濕性關節炎、全身性紅斑狼瘡（包括腎外紅斑狼瘡和紅斑腎炎）的患者隊列之間的嚴重感染率分別為每1000人年22.7、28.7、70.6、43.4和215.3。在美國，一般人口和患有原發性膜性腎病、類風濕性關節炎、全身性紅斑狼瘡（包括腎外紅斑狼瘡和紅斑腎炎）的患者隊列之間的嚴重感染率分別為每1000人年2.6、9.0、15.6、21.0和63.3。在兩種環境下，患者的嚴重感染率都顯著高於一般人口，主要是由細菌、呼吸道、泌尿道和機會性感染引起。患有狼瘡性腎炎的患者相對於一般人口有最高的嚴重感染負擔，其在台灣和美國的調整風險比分別高達7倍至25倍。

結論：這項研究發現，與台灣和美國的一般人口相比，患有特定自體免疫病的患者有顯著的嚴重感染過剩負擔。

Introduction：Serious infections are an important concern for patients with autoimmune conditions. We sought to estimate serious infection rates among patients with select autoimmune conditions relative to the general population in Taiwan and the USA.

Methods：This retrospective cohort study estimated setting-specific standardized serious infection incidence rates and ratios among patients with systemic lupus erythematosus, including extra-renal lupus and lupus nephritis, rheumatoid arthritis and primary membranous nephropathy, compared with the general population using insurance claims for hospitalizations between 2000 and 2013. Multivariable

Cox proportional hazard models were used to estimate adjusted hazard ratios for serious infections, adjusting for age, sex, index year, prior serious infection, comorbidities and medications.

Results：In Taiwan, serious infection rates were 22.7, 28.7, 70.6, 43.4 and 215.3 per 1000 person-years among the general population and among cohorts of patients with primary membranous nephropathy, rheumatoid arthritis, extra-renal lupus and lupus nephritis,

respectively. In the USA, serious infection rates were 2.6, 9.0, 15.6, 21.0 and 63.3 per 1000 person years among the general population and among cohorts of patients with primary membranous nephropathy, rheumatoid arthritis, extra-renal lupus and lupus nephritis, respectively. Patients had significantly higher serious infection rates than the general population in both settings, largely driven by bacterial, respiratory, urinary tract and opportunistic infections. Patients with lupus nephritis had the highest burden of serious infections relative to the general population, with 7- to 25-fold higher adjusted hazard ratios in Taiwan and the USA, respectively.

Conclusion：This study identified a significant excess serious infection burden among patients with targeted autoimmune conditions compared with the general populations in Taiwan and the USA.

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運用人類肺癌細胞及其抗化療細胞分析沒食子酸月桂酯的抗肺癌機制

Analysis of the anti-cancer mechanism of lauryl gallate using human lung cancer cells and their chemoresistant sublines

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過去研究已發現沒食子酸酯類的植化素具有抗氧化和抗發炎特性，其中沒食子酸(Gallic acid, GA)及其衍生物沒食子酸酯可作為食品抗氧化添加劑，應用其清除自由基的能力抑制食油與脂肪的氧化和酸敗。許多研究也證實此類植化素可以清除細胞中的活性氧(ROS)，同時能透過增強氧化壓力(oxidative stress)而促使癌細胞凋亡，而不同烷基鏈長度的沒食子酸酯對細胞也會產生不同程度的細胞毒性。化學療法通常以產生過量的ROS誘發癌細胞嚴重損傷而消滅癌細胞，然而卻常因癌細胞產生抗藥性而導致失效。所以本計畫試驗不同烷基鏈長度的沒食子酸酯是否可應用於肺癌治療，利用具有抗化療的肺癌細胞作為研究實驗模式，探討沒食子酸月桂酯(lauryl gallate, LG, G12)是否可以對肺癌細胞產生高度的細胞毒性或抑制具有抗化療的肺癌細胞生長，並探討沒食子酸月桂酯是經由何種訊息路徑造成抗化療的肺癌細胞的死亡，研究結果發現較長烷基鏈的沒食子酸月桂酯抑制肺癌細胞及其抗化療細胞生長的能力比單寧酸(tannic acid, TA)和沒食子酸辛酯(octyl gallate, OG, G8) 更強，實驗數據也顯示LG具有促使抗化療肺癌細胞凋亡及增加自噬的能力，同時也發現LG 誘發MAPK家族中的p38 kinase和PI3K-Akt信號路徑中的Akt表現高度磷酸活化。綜合以上結果，本研究計畫發現具有較長烷基鏈長度的LG可誘導細胞凋亡和增加自噬，具有抑制抗化療肺癌細胞生長的能力。

Gallic acid (GA) and its ester derivatives, such as lauryl gallate (LG, G12) and octyl gallate (OG, G8), are phenolic acids of plant metabolites spread in most plants. They can inhibit the oxidation and rancidity of oils and fats because of their free radical scavenging and antioxidant activities. Therefore, they can be used as additives in the food industry. GA and its derivatives have also been shown to actively against several types of cancer cells and induce apoptosis. Apoptosis induced by them may be associated with oxidative stress derived from reactive oxygen species (ROS) that indicate these molecules played a role as a pro-oxidant in cancer cells. On the contrary, they also act as natural antioxidants involved in both inhibitory and scavenging actions of ROS. Interestingly, the length of the alkyl chain may exert different mechanisms of cytotoxicity on the target cells. In general, chemotherapy elevates intracellular levels of ROS and promotes cancer cell death. Therefore, we test the cytotoxicity of tannic acid (TA), octyl gallate (OG, G8), and LG using lung cancer and chemoresistant sublines. Then, the effect of LG-mediated cytotoxicity on chemoresistant lung cancer cells was investigated. The results showed that LG has a better anti-cancer effect than TA and OG. The

data also suggested that LG with a long alkyl chain promotes the p38-MAPK phosphorylation, and the Akt of PI3K-Akt signal pathway has also been activated. The data also demonstrated that LG not only induces apoptotic cell death but also enhances autophagy. In sum, the alkyl chain length associated with LG cytotoxicity and LG induces apoptotic cell death and autophagy in lung cancer A549 and chemoresistant sublines.

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社區老年人接種COVID-19疫苗之經驗-質性研究

Experiences of Receiving the COVID-19 Vaccines among Community Elderly Adults: A Qualitative Study

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嚴重特殊傳染性肺炎（COVID-19，簡稱新冠肺炎）大流行給全球人民造成了前所未有的破壞和痛苦，對老年人造成了不成比例的損失。世界衛生組織（WHO）建議老年人接種COVID-19疫苗。然而台灣有許多未接種疫苗的老年人。截至2021年3月29日，台灣有近30% 的75歲以上老年人完全未接種疫苗。然而疫苗接種的決定因素可能很複雜，涉及社會和文化因素，鮮少有關於老年人接種 COVID-19疫苗的看法、猶豫和動機的研究。本研究目的旨在探討社區老年人對接種COVID-19疫苗，其對COVID-19的知識、風險認知、接種的看法或猶豫或社會規範和重要他人的激勵和障礙的影響。採質性研究設計，以立意取樣，收集中部某醫學中心所經營的社區中，於2020年12月時已屆滿的65歲以上之老年人為樣本，以半結構式深度訪談方式進行。自2023年7月26日至12月12日止共訪談18位老年人，呈現資料飽和。訪談內容以錄音記錄並依內容分析法加以分析歸納資料。社區老人在疫情期間，對於接種COVID-19疫苗的經驗感受及看法，包含兩主題與六個次主題：一、認知疫情與危機感：（一）對新冠肺炎的認知不同、（二）意識新冠肺炎的危害、（三）接受COVID-19疫苗的必要性；二、依經歷與風險評估疫苗接種：（一）明確資訊來源影響接種決定、（二）對新冠肺炎疫苗的不確定感、（三）個人疾病與他人經歷影響接種決定。期藉由本研究結果，能提供醫療人員瞭解社區老人接受COVID-19疫苗接種的決定是一個複雜的考慮因素，他們願意接種疫苗以及障礙的經驗，可作為衛生當局設計老年人疫苗接種推廣策略之參考。

關鍵詞：嚴重特殊傳染性肺炎、大流行、疫苗、經驗、質性研究

The COVID-19 pandemic has caused unprecedented devastation and suffering globally, disproportionately affecting the elderly population. The World Health Organization (WHO) recommends COVID-19 vaccination for the elderly. However, there are many elderly individuals in Taiwan who have not been vaccinated. As of March 29, 2021, nearly 30% of individuals aged 75 and above in Taiwan have not received any COVID-19 vaccine. The decision-making factors for vaccination can be complex, involving social and cultural factors. There is limited research on the perspectives, hesitations, and motivations of the elderly regarding COVID-19 vaccination. This study aims to explore the impact of various factors on

the vaccination decision-making process among community-dwelling elderly individuals. These factors include knowledge about COVID-19, risk perceptions, attitudes or hesitations towards vaccination, social norms, and the influence of significant others. The research adopts a qualitative study design, employing purposive sampling. The sample consists of individuals aged 65 and above from a community served by a medical center in central Taiwan, who reached 65 by December 2020. Semi-structured in-depth interviews were conducted from July 26, 2023, to December 12, 2023, involving 18 elderly participants, reaching data saturation. The interviews were recorded and analyzed using content analysis. The experiences and perspectives of community-dwelling elderly individuals during the pandemic regarding the COVID-19 vaccination are categorized into two main themes with six sub-themes: (i) Recognizing the pandemic and acknowledging the crisis: (a) having different knowledge of COVID-19, (b) being aware of the dangers associated with COVID-19, and (c) perceiving the necessity of receiving the COVID-19 vaccine; (ii) Engaging in vaccine decision-making based on experiences and risk assessment: (a) considering the influence of clear information sources on vaccination decisions, (b) being uncertain about the COVID-19 vaccine, and (c) assessing the impact of personal and others' experiences on vaccinating. The results of this study aim to provide healthcare professionals with insights into the complex considerations that influence the vaccination decision-making process among community-dwelling elderly individuals. The experiences of their willingness to receive the vaccine and the barriers encountered can serve as valuable references for health authorities in designing strategies to promote COVID-19 vaccination among the elderly.

Keywords: COVID-19, pandemic, vaccines, experiences, qualitative study

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口腔機能訓練對住院高齡病患之吞嚥功能及口腔健康生活品質之成效

Evaluating the Impact of Oral Motor Function Training on Swallowing Function and Oral Health-Related Quality of Life in Hospitalized Elderly Patients

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口腔健康與高齡者的身體、心理、及社會健康密切相關，甚至影響到生活品質。老化的影響常見口水不足、口腔機能衰退等問題，因此，老年人經常會有咀嚼、吞嚥功能退化的問題。本研究目的主要探討短期口腔機能訓練對住院老年病患吞嚥功能的成效，採類實驗研究設計(Quasi-experimental research design)，以中部某教學醫院高齡科病房篩選出輕度吞嚥困難病患為研究對象，符合條件之老年病患，分為實驗組(n=30人)與對照組(n=30人)。對照組給予衛教單張，實驗組給予健口操，每天三次，餐前執行，一次9分鐘，連續5天。使用改變量進行雙組獨立樣本t檢定，發現在口乾（t=-.320, p=.750）、口水PH值（t=1.296, p=.200）、吞嚥頻率（t=-.132, p=.896）、功能性口服量表(FOIS)（t=-1.157, p=.252）沒有顯著差異。口腔健康評估（t=2.623, p=.011）與口腔生活品質（t=-2.045, p=.045）有顯著差異。故本研究結論，在高齡病患住院期間，實施短期口腔機能訓練，可以促進口腔健康並提升口腔健康生活品質。

關鍵詞：口腔機能訓練、高齡、吞嚥功能、生活品質

Oral health is closely related to the physical, psychological, and social health of the elderly and even affects their quality of life. Common effects of aging include insufficient saliva and decline in oral function, leading to problems such as chewing and swallowing difficulties in the elderly. The purpose of this study was to investigate the effectiveness of short-term oral function training on swallowing function in hospitalized elderly patients. A quasi-experimental research design was adopted, and elderly patients with mild swallowing difficulties were selected from the geriatric ward of a teaching hospital in central Taiwan as the study subjects. Eligible elderly patients were divided into an experimental group (n=30) and a control group (n=30). The control group received educational leaflets, while the experimental group received oral exercises, performed three times a day before meals for 9 minutes each time, continuously for 5 days. Independent samples t-tests were conducted for the change scores, revealing no significant differences in mouth dryness (t=-.320, p=.750), salivary pH (t=1.296, p=.200), swallowing frequency (t=-.132, p=.896), and Functional Oral Intake Scale (FOIS) (t=-1.157, p=.252). However, significant differences were observed in oral health assessment (t=2.623, p=.011) and oral health-related quality of life (t=-2.045,

p=.045). Therefore, the conclusion of this study is that implementing short-term oral function training during hospitalization for elderly patients can promote oral health and improve oral health-related quality of life.

Keywords：Oral function training, Elderly, Swallowing function, Quality of life

TCVGH-HK1128012

下肢截肢病人復原力、社會支持與生活品質之縱貫性追蹤研究

Resilience, Social Support, and Quality of Life Among Patients with Lower Limb Amputation: A Longitudinal Study

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背景：下肢截肢手術會帶來病人及家庭系統衍生出許多複雜的生心理問題及變化，目前國內針對本土下肢截肢病人的復原力、社會支持、生活品質等探討則尚未知，期望能深入了解患者在截肢後各時期的心理調適與復原力變化，提供醫療人員日後照護參考，成功偕同病人重返正常社會生活。目的：本研究欲探討接受下肢截肢病人復原力、社會支持與生活品質之變化。方法：採縱貫式研究設計，以方便取樣招募36位下肢截肢個案，資料收集共四次，以「人口學基本屬性量表」、「中文版Connor-Davidson復原力量表」、「醫療社會支持量表」及「臺灣簡明版世界衛生組織生活品質問卷」，採用重複測量的縱貫性研究設計，以單組重複測量的方法收集資料。結果：研究發現下肢截肢男性病人(P=0.01)、截肢部位(膝下截肢，P=0.017)與復原力呈正相關，社會支持則無顯著差異，生活品質的生理範疇部分，則隨著截肢時間而有顯著改善(P值由0.502轉為0.033)，且最為影響的為膝上截肢病人(P=0.029)；而心理範疇則是截肢部位(膝上截肢及踝部截肢)呈顯著差異。結論與建議：研究結果證實下肢截肢病人的生理層面隨著時間逐漸復原，而膝上截肢的病人在截肢後半年內確實有較大的生理症狀及心理困擾，建議臨床專業人員應加強注意病人有無疼痛、焦慮等生心理相關問題，進而提升照護品質。

關鍵詞：下肢截肢、縱貫性、復原力、社會支持、生活品質

Background: Lower limb amputation surgery will bring about many complex physical and psychological problems and changes in the patient and family system. At present, domestic research on the resilience, social support, quality of life, etc. of local lower limb amputation patients is not yet known. We hope to gain an in-depth understanding of the patients. The changes in psychological adjustment and resilience in various periods after amputation provide medical staff with a reference for future care and successfully help patients return to normal social life. Purpose: This study aims to explore the changes in resilience, social support and quality of life of patients undergoing lower limb amputation. Methods: A longitudinal research design was adopted to recruit 36 lower limb amputation cases through convenient sampling. Data were collected four times, using the "Basic Demographic Attributes Scale", "Chinese Version of Connor-Davidson Resilience Scale", and "Medical Social Support". Scale" and the "Taiwan Short Version of the World Health Organization Quality of Life Questionnaire" adopted a repeated measurement longitudinal

research design to collect data using a single group repeated measurement method. Results: The study found that male patients with lower limb amputation (P=0.01), amputation site (below-knee amputation, P=0.017) were positively correlated with resilience, but there was no significant difference in social support. The physiological category of quality of life increased with the time of amputation. There was a significant improvement (P value changed from 0.502 to 0.033), and the patients with above-knee amputation were most affected (P=0.029); in the psychological category, there was a significant difference in the amputation site (above-knee amputation and ankle amputation). Conclusion and suggestions: The research results confirm that the physiological level of patients with lower limb amputation gradually recovers over time, and patients with above-knee amputation do have greater physiological symptoms and psychological distress within six months after amputation. It is recommended that clinical professionals should pay more attention to the symptoms of patients. There will be no pain, anxiety and other physical and psychological related problems, thus improving the quality of care.

Keywords：Lower limb amputation, longitudinality, resilience, social support, quality of life.

榮東計畫

TCVGH-T1127801

以人工智能預測急診血行性感染病人臨床預後的表現

Using Artificial Intelligence to Predict the Clinical Prognosis of Patients with Bloodstream Infection in the Emergency Department

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在這幾年，AI的應用開始盛行全球，有許多的不同領域的資料被應用在機器學習，透過機器學習的各種演算法來進行預測或者判斷,此研究是以臺中榮民總醫院2012~2021共十年的急診血行性感染病人的資料為基礎，建立一個能夠以急診血行性感染病人的各種數據來建立一個預測死亡率(mortality)的模型，我們的目標是協助醫師做出精確的預測。我們會先針對病人的各種資料數據，有類別變數、連續變數以及病人主訴等記錄，進行整合等資料清洗，使用羅吉斯回歸、XGboost、隨機森林、決策樹以及lightgbm等機器學習的演算法建立預測模型，再以缺失森林、KNN與MICE演算法加上變數的重要因子分析，進行補遺漏值以提升模型的死亡預測準確率。最後的預測方面，缺失森林加上lightgbm的模型預測準確率皆達到了84.3%，以此協助醫師提高死亡預測準確率，進而及早介入治療，達到降低急診血行性感染死亡率(mortality)的目標。

關鍵詞：機器學習、血行性感染、隨機森林、缺失森林、KNN、MICE

In recent years, the application of AI has become prevalent worldwide, with data from various fields being utilized in machine learning. Through various machine learning algorithms, predictions or judgments are made. This study is based on the historical data of emergency patients with bloodstream infection from Taichung Veterans General Hospital between 2012 and 2021. The goal is to establish a model to predict the mortality rate based on various data of patients with bloodstream infection to improve accurate diagnosis and clinical outcome. The raw data, including categorical variables, continuous variables, and medical information such as patients' complaints, will be subjected to data cleaning, integration, and analysis. Machine learning algorithms such as logistic regression, XGboost, random forest, decision tree, and lightgbm will be employed to build predictive models. To improve the model's accuracy, missing data will be addressed using techniques like missing forest, KNN, and MICE, and along with an analysis of variable important factors. In terms of prediction, the model combining missing forest with lightgbm can achieve an accuracy of 84.3%. This model can assist physicians to improve the accuracy of diagnosis and the efficiency of management to reduce the mortality rate associated with bloodstream infection.

Keywords：Machine learning, bloodstream infection, random forest, missing forest、KNN、MICE

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長期使用抗生素對於焦慮行為之影響

Effects of chronic antibiotic use on anxiety-related behavior

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腸道微生物群協助人體生理調節各方面功能，且容易受到飲食與藥物（如抗生素）而改變。腸道菌失衡會影響腸-腦軸的訊息交流，引起大腦功能改變（包括情緒處理）。研究表明，在情感障礙的患者和壓力相關嚙齒動物模型中腸道菌群顯著改變。因此，我們假設腸道菌群失衡通過壓力反應系統導致情緒的變化。而異常焦慮與多種神經精神疾病有關，而腸道菌群對焦慮相關行為的影響在需多研究中並未得到一致的結果。因此，本研究旨在確定抗生素引起的腸道菌失調對焦慮相關行為的影響，並闡明其潛在機制。我們使用抗生素混合物 (ABX) 治療誘導小鼠微生物群失調。結果表明，在接觸抗生素 4 週後，ABX 小鼠表現出更多的焦慮相關行為，並且通過糞便細菌移植 (FMT) 對 ABX 小鼠的腸道微生物群進行再定植可緩解小鼠升高的焦慮行為。 與藥物載體組對照相比，ABX 小鼠在暴露於新環境時，在基底外側杏仁核 (BLA) 中表現出更高的神經元活動，在內側前額葉皮層 (mPFC) 中表現出較低的神經元活動。 抗生素治療引起的過度焦慮與血清皮質酮 (CORT) 水平升高有關，然而，用Metyrapone (50 mg/kg) 阻斷 CORT 合成會使 ABX 小鼠焦慮相關行為有適度改善。綜合上所述，我們目前的數據表明，抗生素引起的腸道菌失調會導致焦慮水平升高，而抗生素治療小鼠的過度焦慮與增強的應激反應和 BLA-mPFC 神經迴路的調節有關。我們的研究結果可以提供一個以抗生素引起焦慮的動物模型，並開發出治療抗生素暴露引起的焦慮表型的創新方法。

關鍵詞：微生物-腸-腦軸、皮質酮、基底外側杏仁核、內側前額葉皮層

Microbiota in the gut is essential to various aspects of physiology, and the microbiome is susceptible to dietary and medicine such as antibiotics. Imbalance of gut microbiota influences gut-brain communication that induces alterations in brain function, including emotional processing. Studies have revealed significant changes in gut microbiota in patients with affective disorder and stress-related rodent models. Therefore, we hypothesize that gut microbiota imbalance leads to emotional changes through stress response systems. Aberrant anxiety is linked with multiple neuropsychiatric disorders; however, the effects of the gut microbiome on anxiety-related behavior are not consistently reported. Thus, this study aims to determine the effects of antibiotic-induced dysbiosis on anxiety-related behavior and to elucidate its underlying mechanisms. We used antibiotics cocktail (ABX) treatment to induce microbiota dysbiosis in mice. The results demonstrated that after four weeks of antibiotic exposure, ABX mice displayed increased anxiety-related behavior, and recolonization of gut microbiota in ABX mice by fecal bacterial transplantation (FMT) rescued elevated

anxiety-related behavior. Compared to vehicle controls, ABX mice exhibited higher neuronal activity in the basolateral amygdala (BLA) and lower neuronal activity in the medial prefrontal cortex (mPFC) upon exposure to novel environments that induced ethologically-based anxiety. Hyperanxiety induced by antibiotic treatment was associated with increased serum corticosterone (CORT) levels; however, blockade of CORT synthesis with metyrapone (50 mg/kg) provoked only modest modifications of the anxiety-related behavior in ABX mice. Taken together, our present data reveal that antibiotic-induced dysbiosis results in increased levels of anxiety, and hyperanxiety in antibiotic-treated mice is associated with enhanced stress response and modulations of BLA-mPFC pathway. Our findings may potentially provide an animal model of antibiotics-induced anxiety and develop innovative approaches to treat the anxiety phenotype induced by antibiotic exposure.

Keywords: microbiota-gut-brain axis, corticosterone, basolateral amygdala, medial prefrontal cortex

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使用生物製劑或JAK抑制劑治療之類風濕性關節炎患者罹患重大心血管事件及靜脈血栓的風險

Risk of major adverse cardiovascular event and venous thromboembolism in patients with rheumatoid arthritis initiating biologics or JAK-inhibitors

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類風濕性關節炎病患得到心血管疾病的風險為一般群眾的 1.5-2 倍。因此找出類風濕性關節炎病患得到心血管疾病的危險因子乃是臨床上重要的議題，且目前仍未有演算法用來預測類風濕性關節炎患者重大心血管事件（major adverse cardiovascular event, MACE）風險。對於對常規合成疾病修飾抗風濕藥 (csDMARDs) 反應不足的 RA 患者，需要使用生物 DMARDs 或靶向合成(ts) DMARDs（即 JAK 抑制劑）進行治療。最近，JAK 抑制劑被證明是有效的，並可以在台灣的醫療保險中報銷。然而，過去關於 JAK 抑制劑是否與 MACE 或靜脈血栓栓塞(VTE)風險增加有關的研究數據仍是相互矛盾的。因此，本研究的目的是使用 2000-2020 年台灣國民健康保險研究數據庫來檢查新接受 bDMARD 或 tsDMARD（即 JAK 抑制劑）治療的 RA 患者其 MACE 和 VTE 風險。

我們共收錄了 12332 名類風濕性關節炎（RA）患者，其中 8902 名患者開始使用 TNF 抑制劑（TNFis），974 名患者開始使用托珠單抗（tocilizumab），994 名患者開始使用阿巴塞普（abatacept），以及 1462 名患者開始使用合成疾病修飾抗風濕藥物（tsDMARDs）。我們發現，2.75%的受試者發展成意外的主要心血管事件（MACE），以及 1.05%發展成意外的靜脈血栓栓塞（VTE）。在 MACE 方面，與 TNFis 相比，沒有任何 b/tsDMARDs 顯著增加風險，而男性性別、b/tsDMARDs 開始治療時的年齡、居住在農村地區、包括高血壓、糖尿病、心臟瓣膜疾病、開始治療前的 MACEs 以及使用抗血小板劑等合併症被認為是獨立風險因素。對於 VTE 而言，與 TNFis 相比，沒有任何 b/tsDMARDs 顯著增加風險，而 b/tsDMARDs 開始治療時的年齡、慢性阻塞性肺病以及使用抗凝血劑被認為是獨立風險因素。

結論：這項基於人群的研究發現，在開始使用後的 5 年內，沒有特定的 b/tsDMARDs 與其他藥物相比，與更高的主要心血管事件（MACE）和靜脈血栓栓塞（VTE）風險相關。

關鍵詞：類風濕性關節炎、重大心血管事件，靜脈血栓栓塞、JAK 抑制劑

The risk of cardiovascular disease development in patients with rheumatoid arthritis (RA) was 1.5-2.0 fold higher than general population. Therefore, it is important to find risk factors for cardiovascular disease. In patients with RA who have inadequate response to conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) are indicated for therapy with biological DMARDs or targeted synthetic (ts) DMARDs (i.e., JAK-inhibitors). Recently, JAK-inhibitors were proved to be effective and were reimbursed in Taiwan’s health insurance.

However, prior data regarding whether JAK-inhibitors are associated with an increased risk of MACE or venous thromboembolism (VTE) are conflicting. Therefore, the aim of this study is to examine the risk of MACE and VTE in b/tsDMARDs-naïve RA patients initiating bDMARDs or tsDMARDs (i.e., JAK-inhibitors) using the 2000-2020 Taiwanese National Health Insurance Research Database.

We enrolled 12332 RA patients, with 8902 patients initiating TNFis, 974 patients initiating tocilizumab, 994 patients initiating abatacept, and 1462 patients initiating tsDMARDs. We found that 2.75% of enrolled patients developed incidental MACE and 1.05% incidental VTE. For MACE, no b/tsDMARDs conferred significantly higher risk compared with TNFis, while male gender, age at b/tsDMARDs initiation, residence in rural regions, comorbidities including hypertension, diabetes mellitus, valvular heart disease, MACEs before initiation, and use of antiplatelet agents were found independent risk factors. For VTE, no b/tsDMARDs conferred significantly higher risk compared with TNFis, while age at b/tsDMARDs initiation, chronic obstructive pulmonary disease, and use of anticoagulants were found independent risk factors.

In conclusion, this population-based study found no specific b/tsDMARDs was associated with higher risk of MACE and VTE compared with one another within 5 year after their initiation.

Keywords: rheumatoid arthritis, major adverse cardiovascular event, venous thromboembolism, JAK inhibitor

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牛樟芝萃取物對亨丁頓舞蹈症之保護作用及機轉探討-以NLRP3發炎體為標的

Antcin-H Isolated from Antrodia cinnamomea Suppresses Neuroinflammation through Inhibition of the NLRP3 Inflammasome in a transgenic mouse model of Huntington's disease

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老化是神經退化性疾病的重要危險因子，醫療保健系統面臨的主要挑戰之一就是神經退化性疾病的日益流行以及人口的迅速老齡化。神經退化性疾病是一個緩慢的病變過程，瞭解疾病的起始原因除了可以掌握病情的發展外，還可發展出早期預警指標，幫助病患改善生活品質與減緩疾病的發展過程，以節省整體社會醫療成本。亨丁頓舞蹈症(Huntington’s disease, HD)是一種遺傳性神經退化性疾病，致病原因為第四對染色體內亨丁頓基因(Huntingtin, Htt)出現超過 36 個 CAG 核酸序列的重覆，此過長的序列轉譯出的突變亨丁頓蛋白(mutant HTT, mHtt)堆積物會危害神經元、星狀膠細胞與微膠細胞的功能。我們過去的研究發現 HD 基因轉殖小鼠(R6/2)紋狀體中有較高程度 NLRP3、ASC 與 caspase-1 的表現。在 R6/2 小鼠中給予 NLRP3 抑制劑 (MCC950)可以有效抑制神經細胞的死亡、減低神經發炎反應、改善小鼠運動能力、同時增加小鼠的存活率，這些實驗結果充分支持在 HD 中抑制 NLRP3 可以有效達到神經保護作用，因此開發 NLRP3 發炎體抑制劑是預防與改善發炎相關神經退化性疾病的策略之一。然而，牛樟芝萃取物與 NLRP3 發炎體間的關係至今仍未被清楚研究，Antcin H 是一種天然三萜，從牛樟芝中純化而來，具有多種藥用和藥理活性。本次計畫將以 NLRP3 為篩選測試平台，找出牛樟芝萃取物抑制 NLRP3 發炎體的有效成分與作用機轉，並以 HD 小鼠疾病模式驗證牛樟芝萃取物預防與改善亨廷頓舞蹈症的效果。

Aging is an important risk factor for neurodegenerative diseases. One of the main challenges for healthcare systems is the increasing prevalence of neurodegenerative pathologies together with the rapidly aging populations. Neurodegenerative disease is a slow pathological process, understanding the cause and process of disease can not only grasp the development of the disease but also develop an early warning index and help patients and their families improve their quality of life and reduce social medical costs. Huntington’s disease (HD) is a neurodegenerative disorder caused by the expansion of the CAG repeat in the huntingtin (HTT) gene. When the number of CAG repeats exceeds 36, the translated expanded polyglutamine-containing HTT protein (mutant HTT [mHTT]) interferes with the normal functions of many cellular proteins and subsequently jeopardizes important cellular machineries in major types of brain cells, including neurons, astrocytes, and microglia. Our previously results revealed high NLRP3, ASC, and caspase-1 expression levels in the striatum of R6/2 mice (a transgenic HD mouse model). Systemic administration of MCC950 to R6/2 mice suppressed the NLRP3 inflammasome and increased neuronal survival, extended lifespan,

and improved motor dysfunction in R6/2 mice. This indicates that the NLRP3 inflammasome should be an important indicator in the treatment of neurodegenerative diseases. Therefore, the development of NLRP3 inflammasome inhibitors is one of the strategies to prevent and improve inflammation-related neurodegenerative diseases. However, the potential protective effect of Antrodia cinnamomea and its underlying mechanisms on NLRP3 inflammasome in HD is unclear. Antcin H, a natural triterpene, purified from Antrodia cinnamomea which showed diverse medicinal and pharmacological activities. In this study, we tested the protective action of Antcin H in HD pathogenesis that involves the NLRP3 inflammasome-dependent pathway.

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糖尿病臨床用藥下新穎基因ca8表達改變對葡萄糖代謝和重新吸收的影響

Effects of altered expression of novel gene ca8 on glucose metabolism and reabsorption under clinical medication for diabetes

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碳酸酐酶 8 (CA8) 是碳酸酐酶 (CA) 家族的成員，但缺乏催化 CO2 可逆水合為碳酸氫鹽和質子的能力。 CA8 蛋白序列跨物種高度保留，顯示 CA8 基因產物具有重要功能。CA8 主要在小腦浦肯野細胞中表達，也在人和小鼠的肝、腎、小腸和大腸中均可檢測到。CA8 唯一已知的生化功能是在腦部細胞中調節鈣 (calcium)的信號，然而 CA8 在小腦之外的確切生物功能仍不清楚。先前，我們發現 CA8 過表達會增加葡萄糖攝取和細胞存活，並與神經元細胞和初級神經元的有氧糖酵解有關，這表明 CA8 在葡萄糖代謝中存在尚未確定的新功能。二甲雙胍 (Metformin, Met)常用於治療第 2 型糖尿病患者，對葡萄糖代謝具有多效性。目前已知 CA8 在神經細胞中會影響葡萄糖吸收，但是 CA8 在肝臟及腎臟細胞的功能尚未知，在本計畫中，使用包括 HepG2 和 HK-2 在內的細胞模型以及 C57BL/6J 小鼠，研究糖尿病臨床藥物 Met 對於 CA8 表達的調節，及其對葡萄糖代謝吸收的機制進行研究。我們研究發現在 HepG2 和 HK-2 細胞中，Met 均表現可調節 CA8 表達的特性，而且 Met 可經由轉錄作用調節 CA8 在細胞中的表達。有趣的是，HK-2 細胞及 Hep G2/C3A 細胞中的 CA8 表達受到葡萄糖濃度的影響，然而葡萄糖濃度對於 CA8 的表達調節，在兩種細胞株中則呈現相反的情況，是否與 CA8 分別在腎臟細胞與肝臟細胞中調節葡萄糖吸收與葡萄糖產量的功能有關，目前正進一步分析中。另一方面，研究 CA8 表達在餵食不同濃度 Met C57BL/6J 小鼠的組織分佈時發現，CA8 廣泛表達於肝臟及腎臟皮質，且高濃度 Met 餵食的小鼠，其肝臟中 CA8 的表達顯著下降。延續性研究目前正進一步剖析 CA8 在肝臟及腎臟細胞中，可能存在對葡萄糖代謝及吸收的分子機制。相信我們的研究將可為 CA8 的生理與病理角色，提供重要研究的里程碑。

關鍵詞：碳酸酐酶 8; 二甲雙胍; 葡萄糖濃度; C57BL/6J 小鼠

Carbonic anhydrase 8 (CA8) is a member of the carbonic anhydrase (CA) family but lacks the ability to catalyze the reversible hydration of CO2 to bicarbonate and protons. The CA8 protein sequence is highly conserved across species, indicating the important functionality of CA8 gene products. CA8 is primarily expressed in Purkinje cells of the cerebellum and can also be detected in the liver, kidney, small intestine, and colon in humans and mice. The only known biochemical function of CA8 is to regulate calcium signaling in brain cells, but its exact biological functions outside the cerebellum remain unclear. Previously, we discovered that overexpression of CA8 increases glucose uptake and cell survival, and is associated with aerobic glycolysis in neuronal and primary neural cells. This suggests a

previously unidentified role for CA8 in glucose metabolism. Metformin (Met), commonly used to treat type 2 diabetes, has diverse effects on glucose metabolism. It is known that CA8 affects glucose absorption in neuronal cells, but its functions in liver and kidney cells are unknown. In this project, we use cell models including HepG2 and HK-2, as well as C57BL/6J mice, to investigate the regulation of CA8 expression by the diabetes drug Met and its mechanisms in glucose metabolism absorption. Our studies found that Met can regulate the expression of CA8 in HepG2 and HK-2 cells through transcriptional regulation. Interestingly, the expression of CA8 in HK-2 and Hep G2/C3A cells is influenced by glucose concentration, but the regulation of CA8 expression by glucose concentration shows opposite patterns in the two cell lines. Whether this is related to the differential regulation of glucose absorption and production by CA8 in kidney and liver cells is currently under further analysis. On the other hand, when studying the tissue distribution of CA8 expression in C57BL/6J mice fed with different concentrations of Met, we found widespread expression of CA8 in the liver and renal cortex. Interestingly, the expression of CA8 in the liver significantly decreased in mice fed with a high concentration of Met. Ongoing research aims to further dissect the molecular mechanisms of CA8 in liver and kidney cells, potentially involved in glucose metabolism and absorption. We believe our research will provide a significant milestone in understanding the physiological and pathological roles of CA8.

Keywords: carbonic anhydrase 8; metformin; glucose concentration; C57BL/6J mouse

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3D列印客製化牙根柱設計製作與臨床驗證

Design, Fabrication and Clinical Validation for 3D-printed Customized Post

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在客製化需求、品質與效率的驅使下，數位贋復成為現代牙科市場的一大趨勢，簡化了傳統印模的步驟，直接將牙齒掃描成數位化檔案，使用 CAD 繪製出符合個人化的牙根柱，結合 CAM 與 3D 列印技術製作出客製化的 3DP 牙根柱，數位贋復使資料取得變得更有效率、還減少許多傳統製程所產生的人工誤差。目前臨床大多是使用固定形狀的牙根柱，但每位患者的臨床條件都不同，固定形狀的牙根柱會影響到黏著強度，因此本研究藉由數位贋復繪製完全符合根管形狀的牙根柱，再使用軟體 Ansys Workbench 進行有限元素分析(Finite Element Method, FEM)，模擬 Push-Out Test 並評估客製化 3DP 牙根柱與根管之間的黏著強度，最後再以體外機械測試來驗證模擬的合理性。期望能藉由本研究讓數位贋復在臨床之應用更為穩定，不僅大幅減少原先機械測試所需的時間成本及耗材，還可以避免在前置作業過程中產生的誤差，同時提升品質與效率。整體研究之結果，提供適當模式給牙科醫師作為臨床實務運作之參考。

Driven by the need for customization, quality and efficiency, digital prosthetic restoration has become a major trend in the modern dental market, simplifying the steps of traditional moulding by directly scanning the teeth into digital files. Personalized posts are drawn using CAD and combined with CAM and 3D printing technology to create fully customized 3DP posts. Digital prosthetic restoration allows for more efficient data acquisition and reduces many of the manual errors associated with traditional processing.

At present, fixed shape of posts are mostly used in clinic, but the post shape of each tooth is different, and it can affect the adhesion strength. Thus, this study used digital prosthetic restoration to create posts that perfectly fit the customized root canal shape. Finite element analysis was performed using Ansys Workbench to simulate the Push-Out Test and to measure the adhesion strength between the 3DP post and the root canal after the restoration treatment. Finally, the results of the external mechanical tests were used to verify the validity of the finite element simulation.

It is hoped that by this experiment for more stable application of digital reproduction in clinical applications, which not only significantly reduces the time cost and consumables required for the original mechanical test, but also avoids errors during the pre-processing, and improves quality and efficiency. The results of the study can provide a suitable model for dentists to use as a reference for clinical practice.

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結合白斑症患部自動標記與處方資訊之治療評估系統

A Vitiligo treatment evaluation system combining automatic labeling system and prescription data

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白顛風(白斑症)是最常見的色素沉著症。的在全球人口中，白顛風的患病率從 0.5%到 1%不等，大大影響了從兒童至大人的生活品質。目前已採用各種治療方法治愈這種皮膚病，包括類固醇及分子雷射等。由於缺乏一共識可靠之療效評估方法，使得無法比較不同的治療方法或相同療法對不同病患之療效。去年規劃執行之白斑症患部面積計算評估，主要以弱監督式學習進行患部色差評估，用以建立治療效果評估依據，今年提出將弱監督式面積計算，轉換成未監督式學習，使用 Autoencoder 技術，讓機器自動學習正確的患部面積，大量減輕醫師標記所花費之時間，再輔以療程處方資訊如光照強度及內外用藥物投放等，使用 A-priori 及貝式網路學習萃取處方與有效患部縮減之關聯性，期望可以找出針對白斑症患者最佳之治療方式。計畫成功完成 Autoencoder 之實作及設計，並導入蜂群算法，將影響白斑面積評估之因數，做最佳組合探索。找到之參數可以用之於白斑面積評估，產生一致標準。

關鍵詞：白顛風(白斑症)、弱監督式面積計算、未監督式學習、Autoencoder、貝式網路學習

Vitiligo (vitiligo) is the most common pigmentation disorder. The prevalence of vitiligo in the global population ranges from 0.5% to 1%, greatly affecting the quality of life from children to adults. Various treatments have been used to cure this skin disease, including steroids and molecular lasers. Due to the lack of a consensus and reliable method for evaluating efficacy, it is impossible to compare the efficacy of different treatment methods or the same therapy on different patients. The area calculation and evaluation of vitiligo affected areas planned and implemented last year mainly used weakly supervised learning to evaluate the color difference of the affected area to establish the basis for treatment effect evaluation. This year, it is proposed to convert the weakly supervised area calculation into unsupervised learning, using Autoencoder technology. Let the machine automatically learn the correct affected area, greatly reducing the time it takes for doctors to mark. It is also supplemented by treatment prescription information such as light intensity and internal and external drug delivery, etc., and uses A-priori and Bayesian network learning to extract prescriptions and reduce the effective affected area. Based on the correlation, we hope to find out the best treatment method for patients with vitiligo. We successfully complete the implementation and design of Autoencoder, and introduce the bee colony algorithm to explore the best

combination of factors that affect the assessment of Vitiligo area. The parameters found can be used for Vitiligo assessment to produce consistent evaluations.

Keywords: Vitiligo (vitiligo)、weakly supervised area evaluation、unsupervised learning、Bayessian network

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以術後大鼠模型研究普利斯德注射劑對心肌細胞的粒線體自噬影響

The Effect of Dexmedetomidine on cardiomyocytes mitochondrial autophagy in Rat Surgery Model

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手術引起交感神經系統激活和氧化壓力的平衡，同時伴隨著發炎、內質網壓力和自噬過程等反應。由於活性氧化物主要來自粒線體，因此這些細胞器被認為是氧化壓力的受害者，暗示了氧化壓力與粒線體自噬之間的聯繫。因此，這個項目涉及使用抗焦慮藥物普利斯德注射劑（Precedex；Dexmedetomidine）來確定它是否能減少手術引起的氧化壓力和粒線體自噬的增加，進而預防手術引起的心臟損傷，並研究其機制。

方法：將大鼠分為三組：第一組為對照組（Control），與其他組一同被犧牲。第二組為手術組，大鼠在全身麻醉下進行 10 分鐘手術，手術後 3 小時犧牲。第三組為普利斯德注射劑+手術組（Dex + Surgery），大鼠在麻醉狀態下緩慢注射普利斯德注射劑注射劑（5 μg/kg）半小時，並在注射過程中進行 10 分鐘手術。手術後 3 小時犧牲。並測量（1）心臟超音波。（2）使用 TUNEL 試劑觀察細胞凋亡。（3）血液分析樣本：測量 NO 和 MDA 含量。（4）使用免疫螢光觀察心臟組織中自噬和粒線體自噬的分布。（5）使用穿透射式電子顯微鏡證明心臟組織中粒線體自噬的分布。（6）通過 Western Blot 測定大鼠心臟組織中的粒線體自噬蛋白表現。

結果：在這項研究中，手術會增加血液中的氧化物質（MDA、NO）含量，而注射普利斯德注射劑並未降低這些物質，反而提高了心臟組織中抗氧化酵素（SOD2、UCP2）的表現。手術增加了心臟組織中 PINK1 和 Parkin 的表達，而注射普利斯德注射劑則會減少了它們的表達。儘管手術組的粒線體出現變化並且粒線體嵴減少，但在 Dex + Surgery 組中，粒線體的破壞較少。結果顯示，普利斯德注射劑能通過改善粒線體抗氧化蛋白的表現，減少對粒線體質量控制的影響，保護了心臟免受手術引起的氧化壓力。然而，儘管使用普利斯德注射劑能減少 LC3 II 表現，但對粒線體自噬的影響並不明顯，這需要再進一步的研究。

關鍵詞：手術、普利斯德注射劑、氧化壓力、粒腺體自噬、心臟損傷、免疫螢光染色、穿透式電子顯微鏡

Surgery leads to balanced nervous system activation and oxidative stress, as well as reactions such as inflammation, stress of the endoplasmic reticulum, and autophagic processes. Since reactive oxygen species originate mainly from mitochondria, these organelles are considered victims of oxidative stress, suggesting a link between oxidative stress and mitochondrial autophagy. Therefore, this project involves the use of antianxiety Precedex (Dexmedetomidine) to determine whether it can reduce oxidative stress and increased mitochondrial autophagy caused by surgery, thus preventing stress-induced heart injury, and to investigate the

mechanisms underlying this.

Method: Rats were divided into three groups: The first group is the control group (Control) and is killed along with the other groups.The second group is the surgical group. Rats were operated under general anesthesia for 10 minutes and sacrificed 3 hours after surgery. The third group is Precedex injection + surgery group (Dex + Surgery). Rats were slowly injected with Precedex injection (5 μg/kg) under anesthesia for half an hour, and surgery was performed for ten minutes during the injection. They were sacrificed three hours after surgery. And measure (1) Echocardiography. (2) Observing the cell apoptosis with TUNEL assay. (3) Samples of blood analysis: NO and MDA content. (4) Observing the distribution of autophagy and mitophagy in heart tissues with Immunofluorescence. (5) Proving the distribution of mitophagy cardiac tissue with a transmission electron microscope. (6) The mitophagy protein expressions of rat myocardial tissue were determined by Western Blot.

Result:In this study, surgery increased oxidative substances (MDA, NO) in the blood, while injecting Precedex did not reduce these substances but increased antioxidant enzymes (SOD2, UCP2) in heart tissues. Surgery increased the expression of PINK1 and Parkin in heart tissue, whereas injection decreased their expression. While there were changes in the mitochondria of the surgery group and a decrease in mitochondrial cristae, there was less mitochondrial disruption in those in the Dex + Surgery group. The results showed that Precedex protected the heart from surgical oxidative stress by improving mitochondrial antioxidant proteins and reducing the effects of mitochondrial quality control. However, although LC3 II was reduced, the effect on mitophagy was not significant, indicating that further studies are needed.

Keywords: Surgery, Precedex (Dexmedetomidine), Oxidative Stress, Mitophagy, heart injury, Immunofluorescence (IF), and transmission electron microscope(TEM)

TCVGH-T1127809

使用機器學習和大數據分析建立住院老年人出院後非預期性再住院與死亡預測模組

Using Machine Learning and Big Data Analysis to Establish a Predictive Model for Unanticipated Readmissions and Mortality of Hospitalized Elderly Patients Post-Discharge.

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本研究透過機器學習與大數據分析，建立了預測台灣住院老年人出院後非預期性再住院及死亡的模型。研究聚焦於分析老年人的多重危險因子，如年齡、多重共病、衰弱程度、憂鬱、營養及生活品質等，以預估其出院後再住院與死亡的風險。透過深度神經網絡（DNN）進行數據分析，結果表明，此模型能有效識別高風險的老年患者。此研究不僅提升了對老年人出院後健康風險的認識，而且為醫療人員提供了寶貴的資訊，幫助他們制定更有效的護理及預防策略。此外，研究亦凸顯了機器學習在醫療領域應用的潛力，特別是在針對老年人口進行精確醫療和預防性照護方面。

關鍵詞：機器學習、老年人、再住院預測、大數據分析

This study, through machine learning and big data analysis, established a model for predicting unexpected rehospitalization and death in elderly patients hospitalized in Taiwan. The research focused on analyzing multiple risk factors in the elderly, such as age, multiple comorbidities, frailty, depression, nutrition, and quality of life, to estimate their risk of rehospitalization and death after discharge. Data analysis was conducted using Deep Neural Networks (DNN), and the results indicated that this model is effective in identifying high-risk elderly patients. The study not only enhances understanding of the health risks for the elderly post-discharge but also provides valuable information to medical professionals, assisting them in developing more effective care and prevention strategies. Furthermore, the research highlights the potential of machine learning applications in the medical field, particularly in precision medicine and preventive care for the elderly population.

Keywords: Machine Learning, Elderly, Rehospitalization Prediction, Big Data Analysis.

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運用頭戴顯示裝置改善病患與醫療人員之作業流程

Using Head-Mounted Display to Improve Patients and Physicians Working Process

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本次研究以深吸閉氣放射治療(Deep-Inspiration Breath-Hold, DIBH)作為切入點，醫療人員在治療患者時，會先定位患者後，讓患者控制其呼吸，以配合放射治療；就現況而言，治療過程中往往會透過螢幕或穿戴頭戴顯示裝置(Head-Mounted Display, HMD)，讓病人了解其呼吸週期及治療之總進度，及協助醫護人員定位患者，而 HMD 通常是以虛擬實境(Virtual Reality, VR)的方式來呈現，若以混合實境(Mixed Reality, MR) 的方式，融入人機互動設計將資訊呈現在病患及醫療人員面前，以人因工程的角度審視，使用者可以在治療中能確保環境之即時狀態，有效避免環境變數導致之意外發生，並提升整體醫療品質。

本計畫依醫院現況，使用 strain gauge 偵測呼吸深度並將呼吸波形顯示予病患，著重於滿足病患在進行放射治療時，病患監控自身呼吸波形之使用者經驗目標，透過人機介面設計，使用 ZMET 產出設計指示，設計呼吸波形圖，優化病患判讀資訊之作業，降低病患與醫護人員於放射治療之負擔。

關鍵詞：深吸閉氣放射治療、頭戴顯示裝置、工作研究、人因工程、人機互動設計

During therapy, physician will locate the patient first, then patient have to control its respiration to match the radiation therapy requirement. It often uses screen or head-mounted display to transfer intelligence to inform patient its respiration cycle and therapy process rate. The device also assists physicians to locate the patient, usually HMD performing as virtual reality. By using mixed reality integrated with human-machine interactive to present intelligence forward patient’s and physician’s sight, users can ensure the environment status during the therapy, avoid accident cause by environment variables, and improve the health care quality as the same time.

Based on the current situation of hospital, we using strain gauge to detect breathe than show the respiratory waveform to patient, focus on users’ experience goal of patients monitoring their own respiratory waveforms during therapy, by human-machine interface design, using ZMET to generate design indicators, then creating respiratory waveform charts,

it optimized patient interprets information, reduce the burden of patients and physicians during therapy.

Keywords: Deep-Inspiration Breath-Hold, Head-Mounted Display, Work Study, Ergonomic, Human-Machine Interactive

榮科計畫

TCVGH-NTCNC1128501

探究組織架構與工作因子在不同部門護理人員的職場壓力與睡眠品質之影響-以某醫學中心為例

On the Study of Occupational Stress and Sleep Quality with Respect to Organizational Characteristics and Work-related Factors of Nurses in Different Departments– take a Medical Center as Example

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本研究旨在評估急診室(ER)護理人員的職業壓力，並闡明人口統計特徵和生理訊號的影響。這項自然觀察型橫斷面(naturalistic cross-sectional)研究於 2022 年 2 月至 5 月進行，包括了急診室和外科護理人員。詳細記錄了人口統計因素，包括年齡、教育背景和是否有子女。同時也記錄了職業屬性，包括工作班次、職位等級、月收入。利用開發的資訊系統，精確記錄了生理數據，包括心率(HR)、職業壓力(OS)和睡眠模式。為了獲得全面的理解，使用 Garmin Vivosmart® 4，對 60 位參與者在 90 天內的 OS 進行了詳細記錄。本研究的主要發現包括：(1) 與他們的資深同事相比，年資較少的急診室和外科護理人員展現出較高的 OS 和睡眠品質，(2) 急診室和外科護理人員在日班時段的壓力較夜班和晚班為高，(3) 急診室護理人員的平均 OS 高於外科護理人員，尤其是在晚班時段，(4) 日班的急診室護理人員展現出最高的活動水平，相比之下，他們在晚班和夜班的活動水平較低，(5) 在急診室護理人員中，年輕組別的活動水平高於年長者。關於工作班次和教育背景的進一步分析結果包括：(a) 日班急診室護理人員較其他班次有更好的睡眠品質，但對於外科護理人員而言，這一趨勢並不顯著，(b) 擁有碩士學位的外科護理人員面對了較高的工作壓力水準，但與僅有大學教育背景的同事相比，他們的睡眠品質也比較好。本研究的實證結果強調了工作班次和部門差異對職業壓力和睡眠品質表現的深遠影響。

This study endeavors to assess the occupational stress of emergency room (ER) nurses, elucidating the impact of demographic characteristics and physiological signals. A naturalistic cross-sectional study was conducted over the period from February to May 2022, encompassing ER and surgical nurses. Demographics factors, encompassing age, education, and parental status, were meticulously documented within a comprehensive. Employment attributes, including work shifts, job rank, monthly income, were also documented. Physiological data, encompassing heart rate (HR), occupational stress (OS), and sleep patterns,

were meticulously recorded using the developed information system. To ascertain a comprehensive understanding, OS was meticulously documented over a 90-day period for 60 participants employing the Garmin Vivosmart® 4. Key findings from this study unveiled the following: (1) Junior ER and surgical nurses exhibited higher OS and sleep quality compared to their senior counterparts. (2) Both ER and surgical nurses exhibited higher stress during daytime shifts than evening and night shifts. (3) ER nurses exhibited higher average OS compared to surgical nurses, particularly during the evening shift. (4) ER nurses on daytime shifts exhibited the highest activity levels compared to their evening and night shifts. (5) Among ER nurses, those in the youngest group engaged in higher activity levels than their older counterparts. Further insights regarding work shifts and education were as follows: (a) ER nurses working during daytime shifts reported improved sleep quality compared to other shifts, though such a trend was not significant for surgical nurses. (b) Surgical nurses with a master's education displayed elevated stress levels but also experienced better sleep quality compared to those with a college education. The empirical outcomes of this study underscore the profound influence of work shifts and departmental distinctions on the manifestation of occupational stress and sleep quality.

榮逢計畫

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製備奈米纖維複合安莫西林於藥物釋放及傷口敷料之應用

Preparation of Nanofibers Combined with Amoxicillin for The Applications of Drug Delivery and Wound Dressing

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由於癌症發病逐漸年輕化，各種化療藥物已被廣泛用於治療各種癌症。然而，治療期間藥物輸送通常需要靜脈或口服攝入，導致藥物濃度最初激增，隨後迅速代謝。這種現象造成藥物浪費,加重身體負擔。如果能夠開發出一種能夠延遲化療藥物釋放的機制，則可以促進藥物的逐漸釋放以治療相關癌症。本研究利用簡單的靜電紡絲技術製造負載5-氟尿嘧啶藥物的聚乙烯醇奈米纖維，以研究其藥物釋放能力，並進一步分析靜電紡絲製備奈米纖維的反應條件和材料特性。 最後探討不同濃度的聚乙烯醇、海藻酸鈉和 pH 值對奈米纖維 5-氟尿嘧啶藥物釋放的影響。此外，在研究中也進一步探討在左氧氟沙星與環丙沙星的藥物釋放之效能，並再次證明本研究所製備之奈米纖維在抗生素上同樣具備有良好的藥物釋放效能。由於奈米纖維製造製程簡單且穩定性高，在不同領域的實際應用具備有重要價值。

Due to the progressively younger onset of cancer, various chemotherapy drugs have been extensively employed for treating various cancers. However, drug delivery often entails intravenous or oral ingestion during treatment, leading to an initial spike in drug concentration followed by swift metabolism. This phenomenon results in drug wastage and burdens the body more. If a mechanism capable of delaying the release of chemotherapeutic drugs could be developed, it could facilitate a gradual release of the drug to treat associated cancers. This study utilized a straightforward electrospinning technique to fabricate polyvinyl alcohol nanofiber loaded with the 5-fluorouracil drug to investigate their drug release capabilities. The reaction conditions and material properties of nanofiber prepared by electrospinning were analyzed. Finally, the effects of different concentrations of polyvinyl alcohol, sodium alginate, and pH values on the 5-fluorouracil drug release of nanofiber were studied. In addition, the drug-release performance of levofloxacin and ciprofloxacin was further explored in the study, and it was once again proven that the nanofibers can exhibit good drug-release performance on antibiotics. Due to the simplicity and high stability of the nanofiber manufacturing process, it is of great value for practical applications in different fields.

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人工智慧用於未閉導管的血流動力學之測試與驗證

Testing and Validation of Artificial Intelligence for Hemodynamics of Patent Catheter

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智慧型檢測系統，如心電圖、心臟超聲波以及利用人工智能（AI）技術，例如卷積神經網絡(CNNs)的異常聲音診斷系統,醫療行業在診斷心臟病條件上取得了顯著進步。在過去的幾十年裡，自動分割和分類心音的方法已被廣泛研究。在許多情況下，無論是實驗數據還是臨床數據，都需要帶有心電圖（ECG）標記的聽診圖（PCGs）或從心音的梅爾頻率倒譜系數（MFCC）譜中提取多個特徵以達到使用 AI 方法的更好識別結果。如果沒有好的特徵提取技術，CNN 在分類心音的 MFCC 譜面可能會面臨挑戰。為了克服這些限制，我們對未閉導管心音分析提出了一種膠囊神經網絡（CapsNet）針對訊號異常來辨認心雜音，它可以利用迭代動態路由方法獲得 MFCC 譜特徵的平移等變性層中的好組合，從而提高心雜音分類的預測準確性。我們使用 2016 年 PhysioNet 心音數據庫來訓練和驗證 CapsNet 和其他 CNN 的預測性能。然後，我們收集了自己的臨床聽診場景數據集,以進行超參數的微調和測試結果。CapsNet 通過在測試數據集上達到 90.29%和 91.67%的驗證準確率，證明了其可行性。

The healthcare industry has made significant progress in the diagnosis of heart conditions due to the use of intelligent detection systems such as electrocardiograms, cardiac ultrasounds, and abnormal sound diagnostics that use artificial intelligence (AI) technology, such as convolutional neural networks (CNNs). Over the past few decades, methods for automated segmentation and classification of heart sounds have been widely studied. In many cases, both experimental and clinical data require electrocardiography (ECG)-labeled phonocardiograms (PCGs) or several feature extraction techniques from the melscale frequency cepstral coefficient (MFCC) spectrum of heart sounds to achieve better identification results with AI methods. Without good feature extraction techniques, the CNN may face challenges in classifying the MFCC spectrum of heart sounds. To overcome these limitations, we propose a capsule neural network (CapsNet) for classifying the patent catheter cases, which can utilize iterative dynamic routing methods to obtain good combinations for layers in the translational equivariance of MFCC spectrum features, thereby improving the prediction accuracy of heart murmur classification. The 2016 PhysioNet heart sound database was used for training and validating the prediction performance of CapsNet and other CNNs. Then, we collected our own dataset of clinical auscultation scenarios for fine-tuning hyperparameters and testing results. CapsNet demonstrated its feasibility by achieving validation accuracies of 90.29% and 91.67% on the test dataset.

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以透明質酸-靛氰綠-聚乳酸甘醇酸奈米螢光探針標定內皮淋巴細胞與建立淋巴水腫動物模型之研究

The Study of Hyaluronic acid capped ICG-PLGA Nanoscale Fluorescence Probe for Lymphedema In vitro and In vivo model

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近年來，精準診斷應用於臨床醫學的議題受到矚目，其中治療淋巴水腫的顯微淋巴管靜脈吻合手術則結合循血綠 (Diagno green Inj，ICG) 的螢光影像系統，將 ICG 螢光分子由指縫注射並以近紅外光光源照射下，ICG 分子可即時性提供淋巴管影像，有助於醫師進行精準的診斷。然而，嚴重淋巴水腫的患者，因為肢體淋巴管的阻塞而使淋巴液外溢導致肢體腫脹，導致 ICG 螢光分子無法明確標定淋巴管的位置，提高手術的風險與時間。因此，本研究計畫已成功地合成透明質酸-靛氰綠-聚乳酸甘醇酸奈米膠囊 (HA-ICG@PLGA NPs)，並將其進行人類皮膚角質細胞 (HaCaT)、小鼠淋巴結血管內皮細胞株 (SV40 transformation of lymphatic endothelial cells，SVEC4-10) 以及非免疫抑制雄性大鼠(Sprague-Dawley) 的生物相容性實驗。以不同濃度的 HA-ICG@PLGA NPs (0.075、0.15、0.3、0.6 與 1.2 mg/mL)，經由細胞增殖檢測試劑 (Cell Counting Kit-8 assay，CCK-8) 分析 HaCaT 與 SVEC4-10 的細胞實驗 (in vitro)，結果顯示 HaCaT 細胞皆有高達 95 %以上的細胞存活率，然而，SVEC4-10 細胞在高濃度時 (0.6 與 1.2 mg/mL) 的細胞存活率約為 80%，其他濃度皆為 95 %以上的細胞存活率。隨後，取 HA-ICG@PLGA NPs (0.1 mg) 經由腹腔注射於非免疫抑制雄性大鼠中，分別於 4 與 24 小時之後犧牲進行臟器的 H&E 染色實驗，由肝臟、腎臟與淋巴管組織切片的染色結果皆顯示正常化的細胞生長。接下來我們已規劃將具有高度生物相容性的 HA-ICG@PLGA NPs 進行 SVEC4-10 細胞的螢光標定，以及非免疫抑制雄性大鼠淋巴管的螢光顯影，可望此奈米螢光顯影劑更接近下一階段應用於淋巴水腫螢光造影的臨床試驗。

In recent years, the topic of precision diagnosis in clinical medicine has gained significant attention. Lymphovenous anastomosis surgery for treating lymphedema combines the use of Indocyanine Green (ICG) fluorescence imaging. By injecting ICG fluorescent molecules into the interdigital spaces and irradiating them with near-infrared light, real-time imaging of the lymphatic vessels is achieved, aiding physicians in precise diagnosis. However, in patients with severe lymphedema, where lymphatic fluid overflows due to the obstruction of limb lymphatic vessels, ICG fluorescence molecules cannot clearly mark the position of lymphatic vessels, increasing the risks and time involved in the surgery. Therefore, this research has

successfully synthesized Hyaluronic Acid-Indocyanine Green-Poly(lactic-co-glycolic acid) nanoparticles (HA-ICG@PLGA NPs). These nanoparticles were subjected to biocompatibility experiments using human keratinocytes (HaCaT), murine lymph node vascular endothelial cell lines (SVEC4-10), and non-immunosuppressed male rats (Sprague-Dawley). Different concentrations of HA-ICG@PLGA NPs (0.075, 0.15, 0.3, 0.6, and 1.2 mg/mL) were used, and Cell Counting Kit-8 (CCK-8) assays were employed to analyze cell viability. The results showed a cell viability rate of over 95% for HaCaT cells at all concentrations. However, SVEC4-10 cell viability was approximately 80% at high concentrations (0.6 and 1.2 mg/mL) and over 95% at other concentrations. Subsequently, HA-ICG@PLGA NPs were injected intraperitoneally into non-immunosuppressed male rats with 0.1 mg, and after sacrificing the rats at 4 and 24 hours, organ histopathology experiments were conducted through H&E staining. The staining results of liver, kidney, and lymphatic tissue sections showed normal cell growth. Next, we plan to perform fluorescence labeling of SVEC4-10 cells and fluorescence imaging of the lymphatic vessels in non-immunosuppressed male rats, demonstrating the high biocompatibility of HA-ICG@PLGA NPs. This progress positions the nanofluorescent imaging agent closer to clinical trials for lymphedema fluorescence imaging in the next stage.

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開發新穎多功能藥物釋放之雙層結構奈米纖維傷口敷料，其中外層為PU/PCL結合PVA含薑黃素和奈米抗發炎及抗菌功能之內層

Development of a novel nanofiber wound dressing with multi-functional drug release double-layer structure of the PU/PCL outer layer combined with PVA inner layer containing curcumin and silver nanoparticles for anti-inflammatory and antibacterial purposes

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臺中榮總與逢甲大學實驗研究團隊提出新期程計畫，聚焦於開發製作多功能性藥物釋放雙層傷口敷料，外層為聚氨酯(PU)/聚己內酯(PCL)纖維，內層為聚乙烯醇纖維添加奈米銀和薑黃素，其中外層 PU/PCL 纖維具有良好耐久度、防潑水性、透氣性功能，內層的PVA搭載天然藥物薑黃素與奈米銀顆粒確保加速傷口的皮膚復原及抗發炎的功效。透過 PVA 與戊二醛進行交聯反應，以延長其藥物釋放時間，成為藥物釋放功能之透氣防水外傷貼布材料配方設計。

為了克服薑黃素本身呈現較差的生物利用度和光穩定性的挑戰，本團隊特別通過將薑黃素巧妙地摻入本研究計畫所擬開發的藥物釋放功能之透氣防水外傷貼布材料配方基材，形成靜電紡絲聚合物奈米纖維結構，期能有效解決這類技術問題。

本研究團隊將聚焦及探索靜電紡絲的多功能性以設計雙層非織造結構，令薑黃素順利搭配奈米銀顆粒發揮完整的抗菌和抗發炎作用。相信吾人所擬材料設計以防止傷口的細菌感染，保持足夠的濕潤環境，並可允許氣體交換和營養物質的運輸，達到最大限度地減輕患者遭受的疼痛與困擾，並能加速傷口癒合過程。

關鍵詞：多功能性雙層傷口敷料、藥物釋放、聚氨酯(PU)/聚己內酯(PCL)纖維、PVA 纖維，天然藥物薑黃素，奈米銀顆粒、傷口皮膚復原及抗發炎、透氣防水外傷貼布

The TVGH-FCU research team currently proposes a new project, aiming at the development and fabrication of drug-releasing multifunctional double-layer wound dressings containing the outer layer of polyurethane/polycaprolactone (PU/PCL) fibers combined with the inner layer of polyvinyl alcohol (PVA) adding both silver nanoparticles and natural medicine of curcumin. The outer layer of PU/PCL fiber is associated with good durability, water repellency and air permeability. The inner layer of PVA loaded with natural medicine curcumin and silver nanoparticles is suitable to promote both the skin recovery of wounds and anti-inflammatory effects. Induction of cross-linking reaction between PVA and glutaraldehyde can also increase the drug release time, of which material formulation design eventually offers the breathable and waterproof wound patch material with drug releasing function.

In order to deal with the technical challenges of poor bioavailability and photostability for curcumin used, we tend to incorporated curcumin into the material formulation of the

breathable and waterproof wound patch material with drug releasing function in this project. It's noted that the formation of electrospinning polymer nanofiber structure can effectively tackle such kind of technical issues.

We will focus to explore the versatility of an electrospinning process by designing a bilayer nonwoven structure, thereby the curcumin can be smoothly combined with silver nanoparticles to exert expected antibacterial and anti-inflammatory effects. It is believed that our proposed material design is capable of suppression of bacterial infection around the wounds to a larger extent with a sufficient moist environment for better air breathing and nutrient transport to greatly reduce the pain and distress for patients as well as to speed up the entire wound healing process.

Keywords: multifunctional double-layer wound dressing, drug-releasing function, polyurethane /polycaprolactone (PU/PCL) fibers, PVA fibers, natural medicine curcumin, silver nanoparticles, wound skin recovery and anti-inflammatory effects, breathable and waterproof dressing.

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攝護腺癌CT灌注影像的最佳數據成像時間

The optimal data acquisition time of CT perfusion imaging for prostate cancer

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CT perfusion 是應用於區別攝護腺惡性腫瘤的有效影像檢查工具,因此在臨床上經常使用。為了得到準確的組織血液微灌流數值,CT perfusion 是需要動態長達 3 到 5 分鐘的掃瞄，但由於 CT 是具有輻射傷害的檢查，因此，掃瞄時間越短對病患越有利。過去的論文，經常使用取像頻率每 1 秒 1 次，掃描總長約 50~100 秒的 CT perfusion，對掃描時間長度無所適從。因此，本研究目的即為驗證最佳的 CT perfusion 掃描時間。為了避免拉長時間造成病人劑量過多，我們將原本的 1 秒 1 次長度為 50 秒的檢查，前 50 秒成像每兩秒掃描一次，50 秒到 180 秒成像之間每五秒掃描一次，讓總體之輻射劑量相當於先前的檢查，並沒有因為更改時間而造成病患過多的輻射劑量暴露。然後，將 180 秒的長度分別取 50 秒、80 秒、120 秒、和 180 秒的 CT perfusion,分析哪個長度的 CT perfusion 有最佳區別攝護腺惡性腫瘤的能力。本研究總共收集 33 位攝護腺癌病患，其中 CT perfusion Type 1 有 7 位，Type 2 有 17 位，Type 3 有 9 位。我們圈選攝護腺腫瘤和旁邊的正常組織,計算曲線的 TTP (Time to Peak)、PEI (Positive Enhancement Integral)、MSI (Mean Slope of Increase)。以 external iliac artery (EIA) 做為動脈輸入,並利用 deconvolution model 計算 blood flow (BF)、blood volume (BV)、MTT (Mean transit time),最後以 Johnson-Wilson 計算微血管通透性(PS)。研究結果顯示，50 秒的 CT perfusion 就足夠就可以將不同 Type 曲線的 Tumor 和 Normal 區分開來，而 ROC 分析指出，80 秒的 CT perfusion 對攝護腺癌腫瘤的鑑別診斷最高。在對比長時間 180 秒的 CT perfusion，短時間的 CT perfusion 便以達到較高的診斷，且輻射劑量較少。因此，本研究結果建議，應以 80 秒的 CT perfusion 作為攝護腺癌的檢查。

CT perfusion is an effective imaging tool for differentiating malignant prostate tumors and is therefore frequently used in clinical practice. To obtain accurate tissue blood micro-perfusion values, CT perfusion requires dynamic scanning lasting from 3 to 5 minutes. However, given that CT scanning involves radiation exposure, shorter scanning times are more advantageous for patients. Previous studies often used an imaging frequency of once per second, with total scan durations of approximately 50 to 100 seconds, leading to uncertainty regarding the optimal scan length. Hence, the purpose of this study was to determine the optimal CT perfusion scanning time. To avoid excessive radiation doses to patients due to prolonged scanning times, our study adjusted the initial scan frequency from once every second for the first 50 seconds to once every two seconds, and from 50 to 180 seconds, scans were conducted once every five seconds, ensuring that the total radiation dose remained equivalent to previous examinations without increasing patient exposure. Subsequently, CT

perfusion scans of 50, 80, 120, and 180 seconds in length were analyzed to identify which duration best distinguished malignant prostate tumors.

This study collected data from 33 prostate cancer patients, including 7 with Type 1, 17 with Type 2, and 9 with Type 3 CT perfusion. We delineated prostate tumors and adjacent normal tissue to calculate the curves' Time to Peak (TTP), Positive Enhancement Integral (PEI), and Mean Slope of Increase (MSI). Using the external iliac artery (EIA) as the arterial input and employing a deconvolution model, we calculated blood flow (BF), blood volume (BV), Mean Transit Time (MTT), and finally, microvascular permeability (PS) using the Johnson-Wilson method.

The results indicated that a 50-second CT perfusion scan was sufficient to differentiate between Tumor and Normal curves of different Types. ROC analysis revealed that the 80-second CT perfusion had the highest diagnostic discrimination for prostate cancer tumors. Compared to longer 180-second CT perfusion scans, shorter durations achieved higher diagnostic accuracy with less radiation exposure. Therefore, this study suggests using an 80-second CT perfusion scan for prostate cancer examinations.

榮葉計畫

TCVGH-DYU1128301

蛹蟲草酒萃物抗過敏的療效評估-小鼠異位性皮膚炎模式

Investigation of anti-allergic effects of ethanolic extract from Cordyceps militaris in cockroach allergen-induced atopic dermatitis murine model

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罹患異位性皮膚炎(AD)的人數日益增加，孩童的盛行率約為 0.92-26.6%，成人的盛行率也高達 17.1%。先前我們分別在生體外的角質細胞株，以及小鼠模型證明美國蟑螂主要過敏原 Per a 2 會誘發皮膚過敏發炎反應。AD 的主要治療包括局部保濕、避開特定致敏物質，以及抗發炎藥物。蟲草相關內生真菌廣泛應用於民俗中藥，許多研究證實培養的蛹蟲草是野生冬蟲夏草的替代種，具有抗氧化、抗腫瘤、以及抗發炎等功效。目前實驗室培養的蛹蟲草對於過敏性皮膚炎的功效尚未被證實。本計畫的目標是探討蛹蟲草的子實體萃取物，對於過敏原誘發的小鼠異位性皮膚炎效益評估。我們模擬臨床實際情況，不使用免疫佐劑，單獨將 Per a 2 過敏原塗抹於小鼠腹部皮膚，每週 1 次共 6 次。致敏期間第 2-5 週管餵蛹蟲草水萃取物(WCM)或是酒精萃取物(ECM)，每週 5 天共進行 25 次治療。結果顯示不論是口服 WCM 或 ECM 都可以有效改善小鼠皮膚患部抓癢行為，以及減少皮膚病兆的細胞浸潤。我們的數據提供後續蛹蟲草開發抗過敏藥用的佐證，希望本計畫的執行可以找到新的策略治療過敏性皮膚炎。

Atopic dermatitis (AD) is becoming more common with a prevalence in children ranging from 0.92–26.6% and in adults up to 17.1%. Previously, we demonstrated that cockroach major allergen Per a 2 could induce skin inflammation in both in vitro keratinocyte cell platform and in vivo murine model. The mainstay therapies of AD are topical emollients to restore skin hydration, avoidance of the process-specific sensitizing agents, and anti-inflammatory therapy. Cultivated Cordyceps militaris (CM) has anti-oxidative, anti-tumor, and anti-inflammatory effects as a substitute for wild species. In this study, we aimed to evaluate the therapeutic effects of CM in Per a 2-induced AD mouse. To closely mimic human AD symptoms in response to aeroallergen stimuli, we adopted the sensitization protocol for AD mice with 6 exposures without adjuvant through the repeated brushing of Per a 2 to the skin. Sensitized mice were administered by gavage of CM extracts once a day on weekdays. Our data revealed that a total of 25 doses of water extract of C. militaris (WCM) or ethanolic extract (ECM) significantly ameliorated Per a 2-induced scratch bouts in mice. Treatment with WCM or ECM significantly attenuated Per a 2-induced histopathology alteration and inflammatory infiltration in the skin lesions compared to the PBS group of mice. The preliminary data would provide a reference for the later investigation of C. militaris on the medical use and anti-allergic activity-related mechanisms. More experiments are in the process. Hopefully, through this project, we will be able to find new therapeutic strategies for allergic dermatitis.

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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(第二年)

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

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

本研究目標是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。結果也發現樹豆根酒精萃取物抑制蟑螂過敏原 Per a 2 會誘發 IL-8、 GM-CSF 和 CCL-20 等免疫相關細胞激素。

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. We find that Cajanus cajan Roots could inhibit expression of IL-8, GM-CSF, and CCL-20 induced by American cockroach allergen Per a 2.

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.*

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運動介入於乳癌存活者紫杉醇導致周邊神經病變之成效

Effects of exercise program on taxane-induced peripheral neuropathy in breast cancer survivors

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乳癌發生率逐年上升，紫杉醇類(Taxane)為主要的化學治療藥物之一，Taxane 導致的周邊神經病變造成存活者功能狀態受損、跌倒或生活品質受衝擊；周邊神經病變嚴重時，需減少化學治療藥物的劑量或中止治療，影響癌細胞毒殺效果、增加死亡率。目前尚無可建議臨床應用對周邊神經病變預防或治療具實證、有效的介入措施；亦無美國食品藥品監督管理局或周邊神經病變醫學、護理專業組織建議的處置方法。故本研究之目的在探討運動介入措施在乳癌存活者周邊神經病變之成效。

本實驗型研究以立意取樣，於中部某醫學中心招募 88 名研究個案；先以治療模式及化學治療藥物的種類將個案分層、再隨機分配至運動組或觀察組。納入年滿 20 歲及以上、初診斷為 I~III 期乳癌、預計進行 taxane 化學治療者。排除在診斷、治療前已有周邊神經病變或有規律運動習慣者。研究測量共有 4 次：(T1)化學治療前、(T2)完成第一次 taxane 治療後、(T3)完成 1/2 化學治療後、(T4)完成所有化學治療時。主要依變項為周邊神經病變、神經痛、末梢血流、功能狀態、跌倒與否及生活品質。資料將以 SPSS 22 建檔，以平均值、標準差、頻率及百分比呈現基本資料、醫療相關訊息及主要研究變項之分布。推論性統計則以卡方、廣義估計方程式分析兩組研究成果之變化與差異。

研究措施為 3~6 個月的居家末梢肢體運動，於個案化學治療前到完成治療後期間介入。運動時間為每日共 50 分鐘，十巧手每日執行 4 次、每次 5 分鐘；下肢伯格-艾倫運動每日 2 次、每次 15 分鐘。觀察組個案不限制其活動；但若有多於日常活動的運動量則須加以記錄，完成研究後，會教導末梢肢體運動。

本研究結果運動介入後兩組在主客觀之周邊神經病變及生活品質並未達顯著差異。可能原因為個案流失、拒絕率高，運動執行度僅約 50%。此外，研究過程中運動組個案皆表示於末梢運動後可改善手足麻的情形；但是若為執行或執行未達標，則運動的效果不彰。

關鍵詞：化學治療導致周邊神經病變、末梢肢體運動、末梢血流、功能狀態、跌倒、生活品質、乳癌存活者

The incidence of breast cancer increases yearly. Taxane is one of the main chemotherapy drugs for breast cancer treatment. Taxane-induced peripheral neuropathy (TIPN) impairs breast cancer survivor’s functioning, increases the risk of falls, and impacts quality of life (QOL). As TIPN worsens, there is a need to decrease chemotherapy dosage or to terminate treatment. This may reduce the effect of chemotherapy, in addition to increase survivor’s mortality. Up to date, no evidence-based, effective nonpharmacologic intervention to prevent or manage TIPN. Furthermore, no interventions were recommended by the U.S. Food and

Drug Administration or TIPN expert organization to prevent or treat TIPN. Therefore, the purpose of this study is to examine the effects of an exercise program on the management of TIPN in breast cancer survivors.

This experimental study utilizes purposive sampling to recruit 88 adults, newly diagnosed with stage I~III breast cancer women, and are expected to be treated with Taxane chemotherapy in a medical center located in central Taiwan. Participants will be randomly allocated to experimental or observational group using the two strata: (1) adjuvant or neoadjuvant and (2) paclitaxel, docetaxel or Taxane plus Platinum. Participants who have peripheral neuropathy prior to chemotherapy or regularly exercise are excluded. The four measure time points are as the followings: (T1) before chemotherapy, (T2) after the completion of first Taxane, (T3) the completion of half chemotherapy regimen, and (T4) the completion of chemotherapy. The main outcomes are peripheral neuropathy and neuropathic pain. The blood circulation of extremities, functional status, falls and QOL are also measured. SPSS 22 is used to enter and analyze data. Mean, standard deviation, frequency and percentage are utilized to describe the distribution of sample and research variables. Chi-squared and generalized estimating equation is used to detect the difference and change over time between the two groups.

The 3~6 months home-based extremity exercise program will be intervened between newly diagnosed of breast cancer to the completion of chemotherapy. Participants have to perform a total of 50 minutes exercise including Ten Skilled Hand exercise forth a day, 5 minute each time and Buerger Allen exercise twice a day, 15 minutes each time. The observational group will need to record the extra exercise performed and the exercise prescription will be distributed after the study.

The research results indicate that there was no significant difference between the two groups in peripheral neuropathic changes and quality of life after exercise intervention. Possible reasons for this include case attrition, a high refusal rate, and a exercise compliance of only about 50%. Additionally, during the study, individuals in the exercise group reported improvement in peripheral neuropathy symptoms after completing the prescribed exercises. However, if the exercises were not performed or not carried out to the required standard, the effectiveness of the exercise was limited.

Keywords：Taxane-induced peripheral neuropathy, extremity exercise program, functional status, falls, quality of life, breast cancer survivors

榮暨計畫

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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中之胰島素及青春激素訊號影響雄性果蠅同性偏好的求偶行為

Olfactory insulin and JH signaling are attenuated by ecdysone-responsive microRNAs let-7-C in male-male courtship behavior

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神經和內分泌系統間錯綜複雜的相互作用影響著動物的生理和行為反應。證據顯示在黑腹果蠅的泛嗅覺感覺神經元(olfactory sensory neurons; OSNs)中，無論是抑制蛻皮激素訊號(ecdysteroid signaling)、促進青春激素訊號(juvenile hormone; JH signaling)或胰島素訊號(insulin/insulin-like growth factor signaling; IIS)皆能觀察到雄性間的求偶行為發生。證據顯示這些內分泌訊息在Fru^M (male-specific Fruitless)表現的Or67d、Or47b及Ir84a嗅覺神經元中參與調節雄性間的求偶行為發生。在此計畫中，進一步證實受蛻皮激素訊號正向調節的let-7靶向調節kr-h1、chico下調青春激素訊號及胰島素訊號；同樣受蛻皮激素訊號正向調節的miR-100也靶向調節gce與InR影響青春激素訊號及胰島素訊號。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及mir-100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。

關鍵詞：果蠅雄性間求偶行為、蛻皮激素訊號、青春激素訊號、胰島素訊號、let-7-C microRNAs

The intricate interplay between the nervous and endocrine systems significantly shapes physiological and behavioral responses in animals. Our prior research not only suppressed ecdysteroid signals but also unveiled a direct upregulation of insulin/insulin-like growth factor signaling (IIS) or juvenile hormone (JH) signaling, playing a crucial role in instigating male-male courtship behavior. This phenomenon is particularly evident in olfactory sensory neurons (OSNs) expressing male-specific Fruitless (FruM), such as Or67d, Or47b, and Ir84a. In this study, we present evidence substantiating the role of ecdysteroid-responsive let-7-complex (let-7-C) miRNAs, specifically let-7, mir-100, and mir-125, in the intricate regulation of male-male courtship within FruM+ OSNs. MicroRNA let-7 targets kruppel homolog 1 (kr-h1), an early response gene implicated in JH signaling, as well as chico, a homolog of vertebrate insulin receptor substrates, thereby exerting influence over JH signaling and IIS pathway. Additionally, mir-100 targets gce and InR, also intricately shaping JH signaling and IIS. This

intricate process involves complex molecular interactions, where imbalances in sophisticated endocrine networks influence specific nerve cells, leading to unconventional behavioral responses.

Keywords：Drosophila male-male courtship behavior, ecdysone signaling, JH signaling, insulin signaling, let-7-Complex microRNAs

TCVGH-NCNU1127902

雷射法製作具有磁性及表面增強拉曼散射的奈米粒子來偵測循環腫瘤細胞

Laser-assisted fabrication of both magnetic and surface-enhanced Raman scattering nanoparticles to detect circulating tumor cells

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本研究首次成功利用脈衝雷射誘發光解法(Pulsed laser-induced photolysis, PLIP)合成磁性 Fe_3O_4 奈米粒子,用於可見光光催化分解亞甲基藍(MB)。材料分析顯示,合成的奈米粒子具有 Fe_3O_4 晶體結構，粒徑在 20-50 奈米之間。水溶液中的磁性奈米粒子具有廣泛的可見光吸收，有利於可見光光催化。光催化結果表明,合成的磁性奈米粒子在 180 分鐘白光照射下，MB 降解效率可達 60%。

This is the first report describing the successful synthesis of magnetic Fe3O4 nanoparticles (NPs) for photocatalytic application by pulsed laser-induced photolysis (PLIP). The material characterization showed the crystalline structure of Fe3O4 with particle size of 20-50 nm. The magnetic NPs dispersed in water solution exhibited broad visible-light absorption, which is favorable for visible-light photocatalysis. The photocatalytic results demonstrated 60% methylene blue degradation efficiency by the synthesized magnetic NPs under 180 min white light illumination.

TCVGH-NCNU1127903

共同處理Regorafenib與蛋白酶體抑制劑引發肺癌細胞A549死亡的機制與應用

The underlined mechanisms and application for Regorafenib/proteasome inhibitor-induced cytotoxicity in the lung cancer A549 cells

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蛋白酶體抑制劑（PIs）主要通過誘導大量毒性錯疊蛋白的積累，而被批准用作抗癌藥物。然而，PIs 的治療可能導致在癌細胞中形成次細胞結構，聚集體。聚集體在其 Vimentin 包圍的籠子中隔離錯疊蛋白，並經由自噬體來清除這些被籠子困住的蛋白質毒素。因此，聚集體的產生會減弱 PIs 誘導的細胞毒性，並可能解釋一些癌細胞對 PIs 的抗性。為了克服 PIs 的抗性問題，我們的團隊對目前抗癌處方的藥物進行篩選，以了解它們對聚集體形成的潛在阻斷活性，並發現抗癌藥物 Regorafenib，一種酪氨酸激酶抑制劑，能夠阻斷 PI（MG132）誘導的聚集體形成，並增強 PI 觸發的細胞毒性。為了探索 Regorafenib 抑制聚集體形成的基本機制，我們根據初步發現和文獻回顧提出了一個可能的 aggresome 促進機制，即 FGFR→HDAC6→p38→聚集體形成，而 Regorafenib 可能從源頭抑制 FGFR，故而阻擋聚集體的形成，亦即: Regorafenib ⊣ FGFR→HDAC6→p38→聚集體形成。我們的分析出乎意料地顯示，FGFR 在調節聚集體形成中發揮了負面作用，因為（1）FGFR 抑制劑促進了 MG132 引發的的聚集體形成，（2）A549 細胞處理 bFGF 後抑制了 MG132 誘導的聚集體形成，降低了 HDAC6 等促進聚集體形成的因子含量。為了另外解析 Regorafenib 如何阻滯 MG132 誘導的聚集體形成，我們檢查了與聚集體形成或錯疊蛋白降解有關的幾種細胞因子的蛋白表現量，並發現 Regorafenib 下調了參與將錯疊蛋白運送到聚集體的 c-Myc-HDAC6 axis 和 HSP70-BAG3 複合物，以及用於運送待降解物到自噬體的 Nrf2-p62 axis。雖然 FGFR 並不參與 Regorafenib 所誘導的聚集體形成抑制，但我們的發現，亦即 FGFR 抑制聚集體形成，為解析以FGF為核心的細胞外信號，如何調節聚集體形成開辟了一條道路。

Proteasome inhibitors (PIs) have been approved as anticancer drugs mainly through inducing extensive accumulation of misfolded proteins, which are toxic to cells. However, treatment of PIs may lead to the development of a subcellular structure aggresome in cancer cells. Aggresome quarantines misfolded proteins in its Vimentin-enclosed cage and recruits autophagosome to clear those caged protein toxicants. Hence, the development of aggresome would attenuate PIs-induced cytotoxicity, and may explain the resistance of some cancer cells to PIs. To overcome the resistance issue of PIs, our team had initiated a screening of currently-prescribed anticancer drugs for their potential aggresome-blocking activity, and found that the anticancer drug Regorafenib, a kind of tyrosine kinase inhibitor, blocked the PI,

MG132-, induced aggresome formation and synergized the PI-triggered cytotoxicity. To explore the underlined mechanisms by which Regorafenib inhibits aggresome formation, we have proposed a signaling cascade based on our preliminary findings and literature review, i.e., Regorafenib—l FGFR→HDAC6→p38→aggresome formation, where Regorafenib inhibits FGFR, and the latter transmits signals to the HDAC6-p38 axis during the aggresome forming process. The pipeline of the study is to confirm the hypothesized signaling cascade and develop a multiagent therapy combining Regorafenib or FGFR inhibitor, HDAC6 inhibitor, and p38 inhibitor to trigger cytotoxicity of lung cancer cell A549. Our analyses unexpectedly showed that FGFR played a negative role in the regulation of aggresome formation by showing that (1) FGFR inhibitors promoted MG132-depednet aggresome formation, (2) incubation of A549 cells with bFGF inhibits MG132-induced aggresome formation by reducing the level of aggresome promoting factors such as HDAC6. To Decode how Regorafenib retards MG132-induced aggresome formation, we examined the protein level of several cellular factors contributing to aggresome formation or misfolded protein degradation and reported that Regorafenib downregulated the c-Myc-HDAC6 cascade and HSP70-BAG3 complex engaged in the targeting of misfolded protein to aggresome, and the Nrf2-p62 cascade, the cargo receptor for autophagy. Although FGFR does not mediate Regorafenib-induced blockage of aggresome formation, yet the finding that FGFR inhibits aggresome formation pave a way to the understanding of how the FGF-based extracellular signaling regulates aggresome formation.

榮臺計畫

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專一性預標靶免疫檢查點放射示蹤劑研製

Development of site-specific pretargeting radiotracer for immune checkpoint

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本研究旨在發展預標靶 ImmunoSPECT/PET 造影劑製備，新的造影劑期能改善傳統直接標誌法抗體放射藥物造成病人高體內輻射劑量及背景活度問題。本研究完成建立 Atezolizumab-TCO 抗體複合體及 68Ga-NOTA-Tz 放射性配體的製備及其品管分析。其 Atezolizumab-TCO 抗體複合體打製得化學純度 100%，68Ga-NOTA-Tz 則可達到放射化學產率大於 98%。此外，本研究完成了 68Ga-NOTA-Tz-TCO-Atezolizumab 的體外點擊反應測試；建立利用放射薄層分析及高效液相層析儀進行其放射化學產率及放射化學純度分析。此預標靶 ImmunoSPECT/PET 造影劑研製的初步結果可為進一步最佳化配合提供重要參考。

關鍵詞：生物耦合、預標靶、點擊化學、免疫單光子／正子斷層造影

In order to improve the disadvantage of traditional direct-labeling antibody-based radiopharmaceutical, the novel pretargeting immunoSPECT/PET tracers based on click chemistry strategy will be developed. In this study, the preparation and characterization of Atezolizumab-TCO conjugate and 68Ga-NOTA-Tz radioligand have been finished and established. Among them, chemical purity of Atezolizumab-TCO conjugate can be obtained as 100% and radiochemical yield of 68Ga-NOTA-Tz can be obtained larger than 98%. In addition, the experimental procedure of in vitro binding test between Atezolizumab-TCO conjugate and 68Ga-NOTA-Tz has been established. Results from this project show that it is worth to further improve the drug and application in the future.

Keywords: conjugation; pretargeting; click chemistry; immunoSPECT/PET

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奈米銀石墨烯複合基材應用於血管修復生物相容性之探討

Discussion on the biocompatibility of nano-silver graphene composite substrate in vascular repair

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在生物醫學領域中，石墨烯及其衍生物氧化石墨烯已被廣泛研究，可應用於藥物釋放、基因檢測、生物感測器以及影像分析等多個領域。近期研究指出，將石墨烯與奈米銀結合形成複合材料，對組織工程修復效果優於單獨使用其中一種材料。因此，本研究旨在探討奈米銀修飾的氧化石墨烯在生物組織工程中的應用。首先，將合成具有不同成分比例的高品質奈米銀修飾氧化石墨烯，並進行材料特性分析。接著，將進行生物相容性測試，包括細胞增殖、貼附、分化和移動等生物功能測試。同時，將研究控制奈米銀粒子在石墨烯上的分佈情況，並評估其對幹細胞分化的影響。此外，考慮到石墨烯和氧化石墨烯對細胞分化的不同影響，將合成具有不同氧化（還原）程度的奈米銀複合材料，並研究其對細胞生長和分化的影響。通過此研究，期望開發出新穎且有效的奈米銀複合基材，為未來臨床相關疾病治療提供參考方向。

In the field of biomedicine, graphene and its derivative, graphene oxide, have been extensively studied and can be applied in various areas such as drug delivery, gene detection, biosensors, and imaging analysis. Recent research suggests that combining graphene with silver nanoparticles to form composite materials yields better tissue engineering repair effects than using either material alone. Therefore, this study aims to investigate the application of silver nanoparticle-modified graphene oxide in biotissue engineering. Initially, high-quality silver nanoparticle-modified graphene oxide with different composition ratios will be synthesized, followed by material characterization. Subsequently, biocompatibility tests, including cell proliferation, adhesion, differentiation, and migration, will be conducted. The distribution of silver nanoparticles on graphene will be controlled, and their impact on stem cell differentiation evaluated. Additionally, considering the differential effects of graphene and graphene oxide on cell differentiation, silver nanoparticle composite materials with different oxidation (reduction) degrees will be synthesized, and their effects on cell growth and differentiation studied. Through this research, novel and effective silver nanoparticle composite substrates are expected to be developed, providing reference directions for future clinical treatments of related diseases.

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以影像辨識為基礎的物件比對應用研究-以疏導門、急診滯留人員為例

Application research of object comparison based on image recognition-taking the example of dredging people stranded in outpatient clinics and emergency departments

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本研究計畫探討在人流出入頻繁的地方，如何讓管理人員有效控管人流，當人數到達設定人數限制時，在後台螢幕畫面顯示人流數及壅塞或舒適的情況。本研究運用YOLO(You Only Look Once)進行人流辨識，再加入 DeepSORT(Simple Online and Realtime Tracking with a Deep association metric)追蹤人流移動與壅塞的判斷。

本研究在各個版本的YOLO 中，統整出不同版本辨識下的人流數據及人流滯留狀況，將其進行比較，找出最適合辨識人流的版本，作為最終進行人流辨識的版本，再把辨識完的人物以 DeepSORT 進行人物追踪與停留時間計算，並依照平均每平方公尺的人人數進行壅塞預警管理與發出訊息告知管理人員。若特定人員滯留時間超過設定時間，並也傳遞訊息讓管理人員查看並進行瞭解。

根據實驗和比較的結果，YOLOv5 版本的平均誤差值最低，準確率最佳，平均每分鐘誤差人數為 2.4 人；YOLOv3 版本的平均誤差值最高，準確率最差，平均每分鐘誤差人數為 6 人；YOLOv7 版本雖為較新的版本，但其平均誤差值的表現並不如 YOLOv5，平均每分鐘誤差人數為 3 人。

本研究採用 Jacobs Crowd Formula 的定義，每平方公尺站立 3-4 人為安全人潮流動的底線。當每平方公尺在 2 人以下時，空間為安全舒適；人數在 2-3 人，空間為略為壅擠；當人數超過 4 人以上時，判斷為出現人流壅塞，並應立即通知相關人員應變。

關鍵詞：YOLO、DeepSORT、卷積神經網路、影像辨識、人流

This research project explores how to effectively control the flow of people in crowded places. When the number of people reaches the set limit, the background screen will display the number of people flowing in and the crowding or comfort situation. This study uses YOLO (You Only Look Once) for crowd recognition, and then adds DeepSORT (Simple Online and Realtime Tracking with a Deep Association metric) to track crowd movement and congestion judgment.

In this study, in each version of YOLO, we integrated the people flow data and people flow retention status under different versions of recognition, compared them, and found the version that is most suitable for identifying people flow. As the final version of people flow recognition, the recognition is completed. . People use DeepSORT to track people and calculate their stay time, and conduct congestion warning management and send messages to managers based on the average number of people per square meter. If a specific person stays

longer than the set time, a message will also be sent for management to see and understand.

According to the experimental and comparison results, the YOLOv5 version has the lowest average error value, the best accuracy, and the average number of errors per minute is 2.4; the YOLOv3 version has the highest average error value, the worst accuracy, and the average number of errors per minute is 6; YOLOv7 version Although it is a newer version, its average error value is not as good as YOLOv5, with an average of 3 people making errors per minute.

This study adopts the definition of Jacobs' crowd formula and takes 3-4 people per square meter as the bottom line for safe crowd movement. When the number of people per square meter is less than 2, the space is safe and comfortable; when the number of people is 2-3, the space is slightly crowded; when the number of people exceeds 4 or more, it is judged that there is congestion, and relevant personnel should be notified immediately to deal with it.

Keywords: YOLO, DeepSORT, CNN, image recognition, people flow

榮興計畫

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深度學習導引複雜型側流分析影像輔助判讀之研究-以雙通道糞便潛血之辨識為例

A Study of Image-Aided Interpretation for Complex Lateral Flow Testing by Deep Learning-Take Reading Dual Channels of Fecal Occult Blood for An Example

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側流分析法（Lateral flow，LF）又稱為免疫層析試紙分析（Immunochromatography，ICG），是一項簡便又精準的疾病快速檢測工具。他可以隨時隨地加上檢體，即可以透過肉眼作出判讀。具有使用簡單、低成本、及時的特性，因此，是目前作為傳染性疾病、藥物偵測的最廣泛作為篩檢方式。單一條試紙用以偵測一個標的，是目前常見的篩檢工具，然而，單一試紙定量分析或者較多標的物的複雜型判斷組合，便無法作為居家使用；這對於以居家篩檢為目的計畫，如腎臟疾病或糖尿病尿液成份長期監控或者大腸直腸癌的居家快篩等，造成阻力。為了解決這個問題，計畫以雙通道糞便潛血為例，以影像搭配深度學習方法來進行雙通道條狀顏色判讀，其步驟包含區域偵測與結果辨識，以完成雙通道糞便潛血之判讀系統。計畫以雙通道糞便潛血試紙之奈米金的標準色澤進行分類建模。接著透過糞便潛血標準品製作 50ng/ mL 與 200ng/mL 兩種糞便潛血的偵測閾值試紙，並植入雙通道反應器內。收集的樣本用來訓練與測試深度學習網路。接著以手機拍攝後並以深度學習網路進行反應結果的判讀。結果顯示在訓練與測試採用不同的反應器外觀與手機時，仍可得到 98.5%以上的辨識效果。此研究成果證實手機拍攝自動判讀性能。

Lateral flow (LF), also known as immunochromatography (ICG), is a simple and accurate strip tool for rapid screening of diseases. It can be interpreted by the eye reading for reaction with sample anytime and anywhere. Since it has the characteristics of easy operation, low cost and timely, it is currently the most widely used screening method for infectious diseases and drug detection. A single testing (T line) on the strip is currently a common screening tool. However, quantitative analysis of a single test strip or a complex combination of multiple T lines suffers from hard reading for household use. That will cause obstruction for long-term monitoring programs such as urine components of diabetes or home-based quick screening for colorectal cancer, etc. To solve this problem, the project proposes image-based deep learning techniques for strip color interpretation. The proposed technique consists of the two steps of deep learning-based region-of-interest detection and classification. The proposed interpretation

system is practically applied to dual-channel fecal occult blood (FOB) test. This project has produced an FOB product and used reactions to artificial hemoglobin to collect test paper samples with detection thresholds of 50ng/ mL and 200ng/mL in a dual-channel reactor. The collected samples are used to train and validate deep learning networks. In test, a mobile phone then takes an image of the project and interprets the result using the trained deep learning networks. The proposed method achieves the test classification accuracy of higher than 98.5% even when using reactors and mobile phones different from those used in training. The results have shown capacity of the mobile phone-based automatic image interpretation system.

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植基於影像切割之深度學習模型及機器學習預測腦瘤患者之無進展生存期

Prediction of Deep Learning model based on Image Segmentation and Machine Learning to Progression-Free Survival Model in Patients with Brain Tumor

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「腦腫瘤（Brain Tumor）」是指腦細胞（Brain Cell）的異常大量生長，部分區域腦組織細胞不正常的生長而形成瘤塊（Tumor），大部分的腦瘤都是由於基因突變（Genetic Mutation）或是損傷所造成的，當腦瘤在頭顱內漸漸增大時必會影響到腦中的其他周圍神經及組織，而影響到其他正常的生理功能，也可能因為腫瘤周圍水腫（Edematous Swelling）腫脹（Tumefaction）而造成顱內壓力增高導致不同症狀產生。本研究透過榮總醫院所提供的腦瘤病患之影像資料及病患病歷資料，並在資料集內新增五種基因欄位IDH、hTERT、MGMT、VEGF、p53。影像資料的部分，利用三種影像切割模型 U-Net、U-Net++、DeepLabV3+模型作訓練，將影像資料進行處理，再藉由深度學習（Deep Learning）切割出腦瘤的確切位置。數值資料的部分利用資料分析（Data Analysis）與機器學習（Machine Learning）技術應用以二元分類模型預測病患是否存活，迴歸模型（Regression Model）用以預測病患的無進展生存期（Progression-Free Survival, PFS）。透過此研究結果與先前未添增新欄位資料集的研究結果進行比較，探討新添加之五種基因之欄位對病人 PFS 及實驗結果之間帶來何種影響。

"Brain Tumor" refers to the abnormal growth of brain cells, and the abnormal growth of brain tissue cells in some areas, resulting in the formation of tumors. Most brain tumors are caused by genetic mutation or injury, and when a tumor grows in the skull, it will affect other peripheral nerves and tissues, and affect other normal physiological functions. When a brain tumor grows in the skull, it will affect other peripheral nerves and tissues in the brain, affecting other normal physiological functions, and may also cause different symptoms due to the increase in intracranial pressure caused by Edematous Swelling (Tumefaction) around the tumor. In this study, we used the image data and medical history of brain tumor patients provided by Veterans General Hospital, and added five new gene fields IDH, hTERT, MGMT, VEGF, and p53 to the dataset, and processed the image data by using three image cutting models, U-Net, U-Net++, and DeepLabV3+ model for training. Deep Learning was used to cut out the exact location of the brain tumor. For the numerical data, a binary classification model is used to predict the survival of the patient using Data Analysis and Machine Learning techniques, and a regression model is used to predict the Progression-Free Survival (PFS) of the patient. The regression model was used to predict Progression-Free Survival (PFS). The results of this study were compared with those of previous studies in which no new columns

were added to the dataset to examine the effects of the newly added columns of the five genes on the PFS of the patients and the results of the experiments.

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建立代謝流質譜追蹤平台研究模式探討捷抑炎療法對體內代謝動態平衡之影響

Establishment of model systems and flux tracing platforms to investigate the metabolic kinetics during tofacitinib therapy

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Tofacitinib 是一種新型的 Janus 激酶 (JAK) 抑製劑，用於治療嚴重的類風濕性關節炎、乾癬和潰瘍性結腸炎。本研究室最近建立追蹤粒線甘氨酸裂解系統的平台，並運用此獨特系統在 2021 榮興計畫 (TCVGH-NCHU 1107602) 中發現抗風濕免疫調節藥物甲氨蝶呤不僅抑制甘氨酸裂解系統的單碳再循環，且會組織特異性地耗盡粒線體單碳供應。此發現提出粒線單碳代謝在免疫發炎調節或藥物副作用中發揮作用的可能性，也對臨床上使用抗風濕免疫調節藥物可能造成其他非標的路徑提出警訊。研究表明，在 Th 細胞刺激的滑膜成纖維細胞中觀察到 JAK 抑製劑抑製糖酵解酶和減少乳酸產生，且會減少滑膜成纖維細胞的葡萄糖轉運蛋白表現以及糖酵解代謝物乳酸濃度，推斷在類風濕性關節炎患者關節中免疫細胞的能量需求增加可能導致檸檬酸代謝物的積累。然而 Tofacitinib 如何影響葡萄糖利用及其在體內不同組織中的碳源分配，以及它如何改變檸檬酸循環和絲氨酸生物合成途徑之間其葡萄糖利用分配則尚未闡明。本研究的目的是研究 Tofacitinib 如何調節調節發炎反應中糖酵解及檸檬酸循環之間的葡萄糖利用。本研究結合細胞和小鼠模型、來自臨床受試者的生化代謝分析、穩定同位素追蹤實驗以及氣相色譜/質譜 (GC/MS) 平台，深入探索 Tofacitinib 如何調節糖酵解、檸檬酸循環碳供應分配和代謝流向，我們研究發現發炎動物模式及 Tofacitinib 交互影響小鼠葡萄糖利用、糖酵解及檸檬酸循環等代謝路徑。本研究協助了解 Tofacitinib 對代謝之深刻影響，對長期接受 Tofacitinib 治療的病患有所助益。

關鍵詞：Tofacitinib；脂肪酸；檸檬酸循環；線粒體單碳代謝；甘胺酸裂解系統；代謝路徑追蹤

Tofacitinib is a novel small-molecule Janus kinase (JAK) inhibitor approved for the treatment of severe rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. Our laboratory recently established a platform for tracking the mitochondrial glycine cleavage system (GCS) and studied the role of GCS in regulating the supply of one carbon (1C) units in the mitochondria. Using this unique system, in our 2021 TCVGH-NCHU project 1107602, we discovered that the anti-rheumatic immunomodulatory drug methotrexate not only inhibited the 1C recycling from GCS, but also tissue-specifically depleted the mitochondrial 1C supply.

These discoveries suggest that mitochondrial 1C metabolism may play an essential role in inflammatory immune regulation or medication side effects. Inhibition of glycolytic enzymes and reductions in lactate production by JAK inhibitors have been observed in Th cell-stimulated synovial fibroblasts. Tofacitinib reduces glucose transporter 1 and the glycolytic metabolite lactate in RA synovial fibroblasts. In the RA joint, the increased energy demand of immune cells may lead to the accumulation of citric acid metabolites. However, how tofacitinib affects glucose utilization and its carbon source allocation in different tissues *in vivo*, and how it can alter the partitioning between citric cycle and glucose derived SSP have never been elucidated. Combining cell and mouse models, data from clinical subjects, stable isotope tracing experiments, as well as gas chromatography/mass spectrometry (GC/MS) platforms, this project provided insight into how tofacitinib may modulate glycolysis and citric acid cycle during inflammation, which will benefit the patients taking tofacitinib.

Keywords：tofacitinib; citric cycle; mitochondria formate; glycine cleavage system; metabolic flux analysis

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研究使用 CD34 濃縮的週邊血球移植對神經壓傷的修復的效應

Outcome of peripheral blood CD 34 enriched monocyte transplantation in nerve crush injury

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背景：奉為圭臬的治療周邊損傷神經的手術包括直接縫合修復，神經移植和神經解離手術。即使是使用現代的手術技術，一些手術的結果也無法達到最佳狀態。在我們以前的研究中，經由 G-CSF 的注射，動員骨髓來源的 CD34 細胞會沈積到損傷的坐骨神經中。而 CD34 細胞沉積增加，VEGF 表達增加以及血管生成/血管生成與神經再生有高度相關行。因此，週邊血球濃縮的 CD34 細胞移植具有分泌血管生成因子的潛力而有助於神經再生的功能。然而，尚未有研究探討週邊血球濃縮的 CD34 細胞(MoFi)在周圍神經損傷中的的效益及細胞表現型的變化。在這項研究中，我們利用週邊血球濃縮的 CD34 細胞，並將其移植到壓傷的神經中，以評估移植細胞的表現型改變，並評估相關的再生和血管生成因子的表達。

方法：在這項研究中，使用血管鉗將 Sprague-Dawley 大鼠（250-300gm）的左坐骨神經壓傷，將動物分為以下三組：第 I 組（假手術）：將傷口切開而暴露左坐骨神經，然後縫合。第二組（C）：把 100 μl PBS 混在 Woven Surgicel 和纖維蛋白膠而包裹壓傷的坐骨神經。第三組（C + MoFi）：把 3x105 MoFi 細胞在 Woven Surgicel 和纖維蛋白膠而包裹壓傷的坐骨神經。然後，對動物進行神經行為評估，電生理研究以及神經和去神經肌肉的再生和血管生成標記的測量。在不同的時間點獲得神經組織，測定 CD31 的血管生成因子，VEGF，von-Willbrand 因子，Isolectin B4 在 MoFi 細胞的表型改變和時間序列及神經再生生物標誌物(S-100 和 NF)的關係。此外使用 DiI 和 FITC 葡聚醣在同一時間點進行了神經血管屏障的測定。

結果：在我們的數據中，未經處理的 MoFi 細胞移植後，神經行為（例如 SFI 和 CatWalk 步態分析）有了顯著改善。這些 MoFi 細胞可以整合到損傷神經中。MoFi 細胞移植可恢復神經形態，增加髓鞘形成，增加髓鞘軸突的數量，增加軸突直徑的比例，從而促進神經再生。所獲得的神經還顯示出血管生成因子的表達，例如 von-Willbrand 和 Isolectin B4 的表達。

建議：根據文獻綜述和我們先前的出版物以及初步數據，MoFi 細胞移植似乎為加速神經再生而提供了血管生成的平台。MoFi 細胞移植具有非細胞操作性的優點，是一項容易完成的任務，可能對臨床應用中的神經修復有益。

關鍵詞：血管增生、單核球細胞、周邊血球、神經壓傷、神經再生

Background: The gold standard surgical treatment for nerve injury includes direct repair, nerve graft, and neurolysis. Even with modern surgical techniques, some operation results may not reach optimal conditions. In our previous publication, bone marrow–derived CD34+ cells

were a dominant cell subpopulation involved in G-CSF–mediated mobilization and deposition into injured sciatic nerves. The increased deposition of CD34+ cells, VEGF expression, and vascularization/angiogenesis paralleled increased nerve regeneration. Thus, the transplantation of enriched CD34 cells (MoFi) from peripheral blood harbored the potential to secrete angiogenesis factors contributing to nerve regeneration. However, the phenotype alteration of transplanted enriched CD34 cells in peripheral nerve injury had not been studied. In this study, we obtained enriched CD34 cells from peripheral blood and transplanted them into the crushed nerve to assess the phenotype alteration in these transplanted cells as well as to assess the associated regeneration and angiogenesis factor expression.

Materials and Methods: In this study, the left sciatic nerve of Sprague-Dawley rats (250-300 gm) was crushed by vessel clamps, and the animals were assigned to three groups as follows: Group I (sham): the left sciatic nerve was exposed and then the wound was closed; Group II (C): the left sciatic nerve was crushed with 100 μl PBS wrapped in Woven Surgicel and fibrin glue over the crush site; Group III (C+MoFi): the left sciatic nerve was crushed with 3x105 CD34-enriched cells (MoFi) wrapped in Woven Surgicel and fibrin glue over the crush site. The animals then received behavior assessment, electrophysiology study, and regeneration and angiogenesis markers of the nerve and denervated muscle. Nerve tissue was obtained at specific time points for the determination of phenotype alteration of these transplanted cells merged with angiogenesis factors of CD31, VEGF, von-Willbrand factors, Isolectin B4, and nerve regeneration biomarkers S-100 and NF. The determination of the nerve-vessel barrier was also conducted at the same time points by DiI and FITC dextran.

Results: There were significant improvements in neurobehaviors such as SFI and CatWalk gait analysis after MoFi cell transplantation. These MoFi cells could integrate into the injured nerve. MoFi cell transplantation could augment nerve regeneration demonstrated by the restoration of nerve morphology and increased myelination. The obtained nerve also showed the expression of angiogenesis factors such as von-Willbrand and Isolectin B4 expression.

Recommendation: MoFi cell transplantation seems to provide a platform for angiogenesis in the acceleration of nerve regeneration. MoFi cell transplantation had the benefit of a non-manipulation procedure and is an easy task, which may be beneficial for nerve repair without ethical considerations.

Keywords：angiogenesis, mononuclear cells, peripheral blood, nerve crush injury, nerve regeneration.

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探討溶瘤家禽里奧病毒調控人外周血單核細胞及誘導胃癌細胞凋亡之分子機轉

Molecular mechanism of oncolytic avian reovirus virus regulation human eripheral blood mononuclear cells and induced gastrc cancer cell apoptosis

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動物病毒可避免人類預先存在之免疫力，同時具有安全性與免疫刺激。除了直接裂解腫瘤細胞外，溶瘤病毒還可以激活免疫反應或被改造以表達治療因子以提高抗腫瘤功效，並逐漸視為一種有效之抗癌方法。四種癌細胞系（A549、AGS、B16F10 與Hela）可被溶瘤家禽里奧病毒 (avian reovirus; ARV)感染並表現高病毒產量。與其他溶瘤病毒一樣，ARV 感染之免疫反應之特點是大量產生促炎細胞因子，包括干擾素-γ(IFN-γ) 與白細胞介素-12 (IL-12)，它們雖會誘導抗病毒作用，但對於啟動先天性和適應性免疫反應至關重要。根據實驗數據顯示，ARV可以sensitization腫瘤壞死因子(tumor necrosis factor; TNF)相關凋亡誘導配體(TNF-related apoptosis-inducing ligand; TRAIL) 表現在初代人先天性和適應性免疫細胞上，在ARV sensitization 下產生 IFN-γ。ARV或紫外線滅活之 ARV (UV-ARV) 可以使人外周血單核細胞 (peripheral blood mononuclear cells, PBMC)表現TRAIL 並殺死AGS，添加可溶性DR5:Fc可阻斷AGS之細胞凋亡，證實是透過 TRAIL 殺死ARV感染之AGS 癌細胞株。ARV或 UV-ARV 可刺激人外周血單核細胞產生IFN-γ，增強細胞免疫功能活化TRAIL表現，透過 IFN-γ/TRAIL 路徑殺死 ARV 感染之AGS 癌細胞株。根據實驗研究成果顯示，免疫反應可以由 ARV 控制，從而增加溶瘤活性。因此，溶瘤ARV具有潛力擴展用於治療癌症和其他惡性腫瘤。

Animal viruses have the possibility to avoid pre-existing immunity in humans, while being safe and immunostimulatory. Besides directly lyse tumor cells, oncolytic viruses can activate immune responses or be engineered to express therapeutic factors to increase antitumor efficacy, and have gradually been recognized as an appealing approach for fighting cancers. Four cancer cell lines (A549, AGS, B16F10 and Hela) can be infected by oncolytic avian reovirus (ARV) and have high virus yield. The immunological response to ARV infection, like many other viruses, is characterized by robust production of proinflammatory cytokines, including IFN-γ and IL-12, which induce a number of antiviral effects and are essential for priming the innate and adaptive cellular components of the immune response. Our data reveal that TNF-related apoptosis-inducing ligand (TRAIL) expression is induced on primary human innate and adaptive immune cells in response to IFN-γ produced during ARV

sensitization. ARV or UV–inactivated ARV (UV-ARV) upregulates PBMC expressing TRAIL preferentially killed ARV-infected AGS and the addition of soluble DR5:Fc blocked the lysis of ARV-infected cells, demonstrating TRAIL-dependent killing of infected AGS cells. The mechanism by which ARV or UV-ARV stimulates human PBMC to kill ARV-infected AGS cancer cells through the IFN-γ/TRAIL pathway and reinforce the importance of IFN-γ produced in response to enhancing cellular immune effector functions. The results revealed that the immune response can be governed by ARV, thereby increasing oncolytic activity. ARV can potentially expand the repertoire of oncolytic viruses for treatment of carcinoma and other malignancies.

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皮膚代謝物在成人異位性皮膚炎致病機轉扮演的角色

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

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背景：異位性皮膚炎是一種慢性復發性的過敏性皮膚病。目前對異位性皮膚炎皮膚病理的了解有限。皮膚代謝物的分析尚未進行。我們的目標是研究異位性皮膚炎患者皮膚的代謝體學。

方法：我們招募了異位性皮膚炎門診患者和健康對照組。使用皮膚膠帶取樣方法收集皮膚中的代謝物。透過 UPLC-MS/MS 代謝體學分析確定差異表現的皮膚代謝物。Mann-Whitney U 檢定用於組間比較。

結果：我們招募了 33 位異位性皮膚炎患者和 39 位健康對照組。我們的結果沒有顯示樣本之間的差異。下一步是改善實驗參數，甚至使用新的分析方法。

結論：總結來說，異位性皮膚炎患者皮膚代謝物的差異表現有望在異位性皮膚炎的發病機制中扮演著至關重要的作用。進一步的分析和機轉研究在得出結論之前仍需要進一步研究。

關鍵詞: 異位性皮膚炎; 代謝體學; 皮膚

Background：Atopic dermatitis (AD) is a chronic relapsing allergic skin disease. The current understandings of skin pathology are limited in AD. Analysis of skin metabolites has not yet been performed. We aim to study the metabolomics in the skin of AD patients.

Methods：We enrolled AD outpatients and healthy controls. Metabolites in their skin were collected using the skin tape strip sampling method. Differentially expressed skin metabolites are determined by the UPLC-MS/MS metabolomics analysis. The Mann-Whitney U test was used to for between-group comparisons.

Results：We recruited 33 AD patients and 39 healthy controls. Our results did not reveal difference between samples. Refinement of the experimental parameters and even use a new analysis method are the next step.

Conclusions：In conclusion, differentially expressed skin metabolites in AD patients are expected to play a crucial role in the pathogenesis of AD. Further analysis and mechanistic studies are required before the conclusion is made.

Keywords：atopic dermatitis; metabolomics; skin

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利格列汀對於肝癌腫瘤的小鼠模式之影響

Effects of linagliptin on the mouse model of hepatocellular carcinoma

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計畫目標：利用動物實驗證明利格列汀抑制肝癌腫瘤的生長並促進凋亡

計畫背景及目的：肝細胞癌是最常見的原發性肝癌類型。肝細胞癌最常發生在患有慢性肝病的人身上，例如由乙型肝炎或丙型肝炎感染引起的肝硬化。二肽基肽酶 4 基因編碼的蛋白質是一種在大多數細胞類型表面表達的酶，與免疫調節、信號轉導和細胞凋亡有關。它是一種 II 型跨膜糖蛋白，以可溶形式存在，存在於血漿和各種體液中。二肽基肽酶 4 似乎在某些腫瘤的發展中起到抑制作用。利格列汀是一種用於治療 2 型糖尿病的藥物。是一種二肽基肽酶 4 抑制劑。它通過增加胰島素的產生和減少胰高血糖素的產生而起作用。先前研究已經在細胞實驗中證明利格列汀能有效抑制肝癌細胞株生長及細胞週期，並同時造成細胞凋亡。本計畫旨在利用動物實驗證明利格列汀對於肝癌腫瘤的療效，並探討二肽基肽酶 4 在血液中的變化與扮演的角色。

研究方法：證明利格列汀對肝癌腫瘤的療效

將 BALB/cAnN.Cg-Foxn1nu/CrlNarl 裸鼠分為三組。異種移植肝癌細胞後給予利格列汀 0、30 和 60 毫克/公斤/天持續 14 天，接著從小鼠身上收集腫瘤和血液樣本進行後續分析。

預期研究成果：我們的先期研究結果證明在細胞實驗中利格列汀會抑制肝癌細胞株生長及造成細胞週期停滯，並誘導細胞凋亡。因此我們想利用動物實驗共同驗證是否與細胞實驗結果一樣具有不錯的療效，這項研究成果將鼓勵糖尿病患者更積極使用二肽基肽酶 4 抑制劑，達到減少肝癌發生的效果。我們將結合細胞實驗的結果，一同發表在優質期刊中。

Study objective: To prove linagliptin inhibits the progression of liver tumors and induces apoptosis in the animal model.

Study background and rationale: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It occurs most often in people with chronic liver disease, such as cirrhosis caused by hepatitis B or C infection. The protein encoded by the dipeptidyl peptidase 4 (DPP4) gene is an enzyme expressed on the surface of most cell types and is involved in immune regulation, signal transduction, and apoptosis. It is a type II transmembrane glycoprotein that exists in soluble form in plasma and various body fluids. DPP4 plays an inhibitory role in the development of certain tumors. Linagliptin is a DPP4 inhibitor and is used to treat type 2 diabetic patients. It works by increasing insulin production and decreasing glucagon production. Previous studies have demonstrated that linagliptin effectively inhibits the growth and cell cycle in HCC cells, and induces apoptosis, simultaneously. This project

aims to use animal experiments to demonstrate the efficacy of linagliptin on liver cancer tumors and to explore the concentrations and roles of DPP4 in blood and tumor.

Study method: Prove the efficacy of linagliptin on liver cancer tumors.

The BALB/cAnN.Cg-Foxn1nu/CrlNarl nude mice were divided into three groups. After xenograft of Hep3B cells, linagliptin will be administered at 0, 30 and 60 mg/kg/day for 14 days, followed by tumor and blood samples collected from mice for subsequent analysis.

Expected study results: Our preliminary results show that linagliptin efficiently inhibits the growth of HCC cells, leads to cell cycle arrest, and promotes apoptosis. Therefore, we expect to examine animal experiments to verify whether it has the similar curative effect as the results of cell experiments. The results of this research will encourage diabetic patients to use DPP4 inhibitors more actively to achieve the effect of reducing the occurrence of liver cancer. We will combine the results of the cell experiments and publish them in a high-quality journal.

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硫酸軟骨素合成酵素在腫瘤微環境中對神經膠質瘤細胞增生與侵襲之研究

Investigation of chondroitin sulfate synthases in glioma tumor microenvironment modulating cancer cell growth and invasion

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超過 50 %的腦膠質瘤是多形性膠質母細胞瘤(GBM)，它是人類中最具侵襲性的癌症之一。最近，我們發現硫酸軟骨素(CS)修飾酶經常在 GBM 過度表達，與較差的生存期有關。這些酶改變癌細胞和腫瘤微環境（TME）CS 的形成，並與細胞生長和侵襲性相關，但其分子機制尚未釐清 。因此，我們假設藉由阻斷 CS 的功能或抑制 CS 堆積的技術具有開發成新療法的潛力。.

我們透過免疫組織化學研究了膠質瘤組織中 CHST11 的表達，並使用公共 RNA 定序資料集分析了 CHST11 相關基因。 CHST11 對攻擊性細胞行為的影響已在體外和體內進行了研究。我們證明 CHST11 在 GBM 組織中頻繁過度表達，促進 GBM 細胞遷移並調節 GBM 細胞上的 C4S。我們進一步發現 CSPG4 與 CHST11 呈正相關，CSPG4 參與 CHST11 介導的細胞侵襲。此外，CHST11 和 CSPG4 高表現的 GBM 患者的存活時間明顯較短。我們在體外和體內檢查了 C4S 特異性結合勝肽 (C4Sp) 作為治療劑的效果。 C4Sp 治療減弱了 GBM 細胞的侵襲性，尤其是提高了原位膠質瘤細胞移植小鼠的存活率。我們的結果提出了 CHST11 調節 GBM 惡性腫瘤的可能機制，並強調了一種針對 GBM 細胞中異常硫酸軟骨素的新策略。

Over 50 percent of glioma is glioblastoma multiforme (GBM), whichis one of the most aggressive human cancers, and the median survival time of afflictedpatients is less than 2 years. Thegoal of our laboratoryis to develop new treatments for human cancersby exploring the rolesofabnormalglycosaminoglycan (GAG) accumulation in tumor microenvironment(TME).

Recently, we focused onchondroitin sulfate(CS)synthases and modifying enzymes, whicharefrequently overexpressed in human gliomasandareassociated with poor survival of patients. We foundthatthese enzymes not only alteredCS formation on cancer cellsand TME, but also promotedcell growth and invasiveness.Thus, we hypothesize that methods for blocking the functions or the accumulation of CS in glioma tissue have great potential to developinto novel treatments for patients with glioma.Such CS-specific targetingapproachesmay modulate the interactions amongtumor cells, TME,and immune cells in glioma tissues.Thus, we proposed twospecific aims for this project as outlined below.

We investigated the expression of CHST11 in glioma tissue by immunohistochemistry, and analyzed CHST11 associated genes using public RNA sequencing datasets. The effects of CHST11 on aggressive cell behaviors have been studied in vitro and in vivo. We demonstrated that CHST11 is frequently overexpressed in GBM tissue, promoting GBM cell mobility and

modulating C4S on GBM cells. We further discovered that CSPG4 is positively correlated with CHST11, and CSPG4 involved in CHST11-mediated cell invasiveness. In addition, GBM patients with high expression of CHST11 and CSPG4 have a significantly shorter survival time. We examined the effects of treating C4S-specific binding peptide (C4Sp) as a therapeutic agent in vitro and in vivo. C4Sp treatment attenuated GBM cell invasiveness and, notably, improved survival rate of orthotopic glioma cell transplant mice. Our results propose a possible mechanism of CHST11 in regulating GBM malignancy and highlight a novel strategy for targeting aberrant chondroitin sulfate in GBM cells.

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臨床前動物試驗-利用原位腦神經膠質瘤小鼠模型評估PEITC之功效與安全性

Preclinical Animal Testing - Evaluating the Efficacy and Safety of PEITC Using an Orthotopic Glioblastoma Mouse Model

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苯乙基異硫氰酸酯（PEITC）是異硫氰酸酯家族中常見的化合物。先前的研究顯示，PEITC 能夠在胰臟癌、卵巢癌和肺癌等癌症中誘導細胞凋亡並抑制細胞生長。

惡性膠質瘤是一種嚴重的腦腫瘤，具有高復發率和不良預後。針對本研究的目的，確定了幾個明確的目標。在這個研究項目中，我們使用了小鼠的原位腦癌模型，並檢查了 PEITC 給藥對腦腫瘤生長的影響。通過原位腦癌小鼠模型，我們分析了 PEITC 治療對生理參數、外周血細胞和腫瘤微環境中免疫細胞種群的影響。

在評估 PEITC 治療對細胞存活能力的影響時，我們觀察到了減少的增殖率和受損的存活能力，表明其具有細胞毒性。我們還專注於研究 PEITC 如何影響細胞侵襲和轉移，這是癌症進展的關鍵階段。此外，我們還研究了 PEITC 治療對免疫細胞水平的影響，特別是骨髓源性抑制細胞（MDSCs）和自然殺手細胞（NK 細胞）。在給予 PEITC 後，我們觀察到治療組中 NK 細胞的數量略有增加，與對照組相比。基於以上結果，我們相信 PEITC 在臨床環境中對腦腫瘤具有潛在的治療潛力。

關鍵詞：苯乙基異硫氰酸酯（PEITC）、神經膠質瘤、自然殺手細胞

Phenethyl Isothiocyanate (PEITC) is a common compound of the isothiocyanate family. Previous studies have shown that PEITC can induce apoptosis and inhibit the growth of cancer cells in pancreatic cancer, ovarian cancer, and lung cancer.

Malignant glioma is a severe brain tumor with a high recurrence rate and poor prognosis. As for the purpose of this research, several precise objectives have been identified. In the research project, we used an orthotopic brain cancer model in mice, and the effects of PEITC administration on brain tumor growth were examined. Through the orthotopic brain cancer mouse model, we analyzed the effects of PEITC treatment on physiological parameters, peripheral blood cells, and immune cell populations within the tumor microenvironment.

To evaluation of cellular viability upon PEITC treatment, we have observed reduced proliferation rates and impaired viability, indicating its cytotoxic properties. We have also concentrated on studying how PEITC affects cellular invasion and metastasis, which are pivotal stages in cancer advancement. In addition, we investigated the effects of PEITC treatment on the levels of immune cells, specifically myeloid-derived suppressor cells (MDSCs) and natural killer (NK) cells. Following administration of PEITC, we observed a

slight increase in the population of NK cells in the treated group compared to the control group. Based on the above results, we believe that PEITC holds promising therapeutic potential for brain tumors in clinical settings.

Keywords: PEITC、Glioma、Natural killer cells

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玻尿酸嫁接非類固醇類藥製成生物可分解材料在術後傷口局部止痛與防沾粘之應用

Application of hyaluronic acid grafted non-steroidal drugs to make biodegradable materials for local pain relief and anti-adhesion in postoperative wounds

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在全球的外科手術中，有絕大部分的案例是使用整形外科或重建手術，嘗試對於因為戰爭、 事故或自然災害所受損的軟組織、肌腱、神經和骨骼進行有效治療。這些受損的組織，若沒有及時得到適當的治療，嚴重時則可能會導致殘疾。而組織損傷、惡性腫瘤或先天性異常等案例， 也可以透過整形手術有效的幫助患者提高自尊、自信和整體生活品質。然而外科手術常會伴隨許多不良情形的發生，例如傷口疼痛、感染，癒後發生組織沾黏、皮膚蟹足腫等後遺症。其中，對於接受治療手術的患者來說，有效緩解疼痛是至關重要的。術後品質管理的目標是以最小的 副作用達到減輕或消除患者之疼痛和不適感。儘管臨床上的治療方式止痛效果較強，但仍無法避免因治療方式所產生之後遺症。玻尿酸作為近年來在醫美上的明日之星，其已被科學家證實除了生物相容性高及具有抗組織沾黏的優勢外，更可以當作藥物載體，同時也因其在結構修飾上具有非常大的彈性，可根據功能之需求做高度的客製化。鑑於臨床上之需求以及玻尿酸之優勢，本計畫目的為開發出具有緩釋止痛藥、抗組織沾黏、止痛效果的玻尿酸非口服材料。預期此材料可以有效緩解病人術後不適與提供較佳的患者依從度。

In the vast majority of surgical procedures worldwide, orthopaedic or reconstructive surgery attempts to effectively treat soft tissue, tendons, nerves and bones damaged by war, accident or natural disaster. These damaged tissues, if not treated properly in time, can lead to disability in severe cases. In cases of tissue damage, malignant tumors or congenital anomalies, plastic surgery can also effectively help patients improve self-esteem, self-confidence and overall quality of life. However, surgical operations are often accompanied by many adverse conditions, such as wound pain, infection, tissue sticking, skin crab foot swelling and other sequelae after healing. Among them, effective pain relief is crucial for patients undergoing therapeutic surgery. The goal of postoperative quality management is to reduce or eliminate patient pain and discomfort with minimal side effects. Although the clinical treatment methods have strong analgesic effect, the sequelae caused by the treatment methods cannot be avoided. As a rising star in medical beauty in recent years, hyaluronic acid has been confirmed by scientists that in addition to its high biocompatibility and the advantages of anti-tissue adhesion, it can also be used as a drug carrier. It is very flexible and can be highly customized according to functional requirements. In view of the clinical needs and the advantages of hyaluronic acid, the purpose of this project is to develop a non-oral material of hyaluronic acid

with slow-release analgesics, anti-tissue adhesion, and pain-relieving effects. It is expected that this material can effectively relieve postoperative discomfort and provide better patient compliance.

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探討imiquimod處理癌細胞後上調免疫檢查點配體HLA-G表達以削弱自然殺手細胞毒殺的機制

Exploring the mechanism of up-regulating the expression of immune checkpoint ligand HLA-G to impair natural killer cell cytotoxicity in imiquimod-treated cancer cells

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免疫檢查點是免疫抑制性受體。當免疫細胞上的免疫檢查點與腫瘤細胞上的免疫檢查點配體結合時，免疫細胞上的共抑制訊號被激活，抑制免疫細胞的功能，使腫瘤細胞能夠逃避免疫細胞的監視。Imiquimod（IMQ）是一種臨床上使用的類鐸受体 7（TLR7）活化劑，可透過間接激活細胞介導的免疫反應或直接誘導癌細胞死亡，表現出抗腫瘤活性。了解 IMQ 是否能夠調節癌細胞中特定的免疫檢查點配體的表達，並藉由特定的免疫檢查點阻斷增強抗腫瘤免疫力是一種具有吸引力的治療策略。因此，本研究將探討 IMQ 處理的癌細胞中誘導的免疫檢查點配體的種類及可能機制。我們發現，在依賴於 ROS 的方式下，IMQ 處理的癌細胞中，包括膜和分泌形式的免疫檢查點配體 HLA-G 的表達顯著增加，並且在 p53 野生型和 p53 突變型癌細胞中均受到轉錄水平的調控。我們證明了 IMQ 處理的癌細胞抑制了 NK 細胞株（一種 NK 細胞系）對腫瘤細胞的殺傷效應。在機制研究中，我們證明了在 TLR7 未表達的癌細胞中，IMQ 可透過 ROS 介導的途徑上調 HLA-G 的表達，β-連接蛋白抑制劑 ICG001 減少了 IMQ 誘導的 HLA-G 上調，並逆轉了 IMQ 對癌細胞中 NK 細胞殺傷的抑制作用。這些證據表明，IMQ 誘導的 ROS 可能通過β-連接蛋白途徑促進 HLA-G mRNA 的表達。除了探索 IMQ 誘導的癌細胞中 HLA-G 上調的分子機制外，這項研究還可能幫助我們開發新的策略，通過將 IMQ 與靶向 HLA-G 的治療結合起來，提高 IMQ 對於癌症治療中的抗腫瘤免疫力，特別是對於 p53 突變型癌細胞。

Immune checkpoints are immunosuppressive receptors. When the immune checkpoints on immune cells bind to immune checkpoint ligands on tumor cells, their co-inhibitory signals are activated to inhibit the function of immune cells, allowing tumor cells to escape the surveillance of immune cells. Imiquimod (IMQ) is a clinical used toll-like receptor 7 (TLR7) agonist that exhibits anti-tumor activity through indirectly activating cell-mediated immune responses or directly inducing cancer cell death. Understanding whether the IMQ could regulate specific immune checkpoint ligands expression in cancer cells and enhancement of anti-tumor immunity by applying specific immune checkpoint blockage is attractive strategy. Thus, we examined what kinds of immune checkpoint ligands are induced in IMQ-treated cancer cells. We found the expression of immune checkpoint ligand HLA-G including membrane and secreted forms was significantly increased in IMQ-treated cancer cells with

ROS-dependent manner and regulated at transcriptional level in both p53 wild type and p53 mutant cancer cells. We demonstrated that the IMQ-treated cancer cells reduced the killing effect of NK92 cells, a NK cell line, on tumor cells. In mechanism study, we demonstrated IMQ up-regulated HLA-G expression with a ROS-mediated pathway in TLR7-unexpressed cancer cells and β-catenin inhibitor ICG001 decreased the IMQ-induced HLA-G upregulation and reversed the IMQ-induced inhibition of NK cells killing in cancer cells. These evidences indicates that IMQ-induced ROS may promote HLA-G mRNA expression through β-catenin pathway. In addition to explore the molecular mechanism of IMQ-induced HLA-G upregulation in cancer cell, this study may also help us to develop novel strategies by combining IMQ with targeting HLA-G therapy to improve the anti-tumor immunity of IMQ for treatment of cancers, especially in p53 mutant cancer cells.

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糖尿病動物衰弱表現型與因子探討

Frailty phenotypes and relevant factors in animal models with diabetes

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衰弱症是一種複雜的、多系統的、與年齡相關的綜合症，它增加對功能退化和不良事件（包括死亡）的脆弱性。糖尿病是一種因胰島素分泌缺陷和胰島素敏感性不良導致高血糖所的代謝性疾病，與衰弱症類似是遺傳因素和後天因素相互作用的結果。據報道，糖尿病患者罹患衰弱症的盛行率高於非糖尿病患者。然而，衰弱症與糖尿病之間的關係複雜，其相關性及機制仍有許多未明之處。因此，透過糖尿病動物模型來研究其相關性，對於介入療法之測試及轉譯至臨床實踐非常重要。本研究目的是在糖尿病小鼠中開發一種與人類臨床標準相符的衰弱症表型（虛弱、行走速度慢、活動量低、耐力差）。以懸吊箱試驗、曠場試驗、滾輪試驗和 Morris 水迷宮試驗評估小鼠的標準。採用高脂飲食和鏈脲佐菌素(STZ)建立糖尿病小鼠模型。 雄性 C57Bl/6J 小鼠（40 週齡）隨機分為對照組（CON，n=15）及糖尿病組（DM，n=15）。第 4 週施用 STZ（30 mg/kg，腹腔注射）或載體。於試驗第 16 週，收集血液和組織樣本進行分析。結果顯示，DM 組的體重、空腹血糖值、胰島素值、HOMA-IR 和曲線下面積(IPGTT)均高於對照組。這表示高脂飲食和 STZ 治療成功誘導了糖尿病動物模型。我們透過評估人類衰弱症使用的臨床標準，比較了 DM 與對照組的虛弱程度：耐力差（跌倒的潛伏期）、緩慢（步行和游泳速度）、虛弱（肌肉質量損失）和活動水平低（運動協調性）。結果顯示，DM 組的跌倒潛伏期和肌肉量均低於對照組，DM 組的步行和游泳速度較慢、運動協調性較差。綜合而之，高脂飲食和 STZ 治療可以有效誘導中年小鼠衰弱，我們的試驗結果提供了一個評估治療介入的平台並及轉譯至臨床實踐。

Frailty is a complex, multisystem, age-associated syndrome that increases vulnerability to functional decline and adverse events, including death. Diabetes (DM) is a metabolic disease of defective insulin secretion in response to glucose and impaired insulin sensitivity defined by hyperglycemia and, similar to frailty, results from the complex interplay of genetic and acquired factors. It is reported that the frailty prevalence in diabetic people is more than that in non-diabetic counterparts. However, the relationship between frailty and DM is complex and several questions remain unanswered. Therefore, the development of diabetic animal models to study this relationship is important to test interventions to be translated to the clinical practice. The aim of this study was to develop a frailty phenotype in diabetic mice that mimicked the clinical criteria used in humans, including weakness, slow walking speed, low activity level, and poor endurance. We utilized various tests such as the wire hanging box test, open field test, rotarod test, and Morris water maze test to assess these criteria in mice. To induce diabetes in the mice, a combination of a high-fat diet and streptozotocin (STZ)

administration was employed. Male C57Bl/6J mice aged 40 weeks were randomly divided into control (CON, n=15) and diabetes (DM, n=15) groups. STZ (30 mg/kg, i.p.) or vehicle was administered on the 4th week, and after 16 weeks of treatment, blood and tissue samples were collected for analyses. The results indicated that the diabetic mouse model exhibited characteristics of diabetes, including higher body weight, fasting blood glucose levels, insulin levels, HOMA-IR, and area under the curve (IPGTT) compared to the control group. This confirmed the successful induction of diabetes in the mice using the high-fat diet and STZ treatment. Furthermore, when comparing the diabetic mice to the control group in terms of frailty, the diabetic mice exhibited lower endurance (measured by latency to fall time), slower walking and swimming speeds, weakness (loss of muscular mass), and poorer motor coordination. Overall, the study concluded that the combination of a high-fat diet and STZ treatment effectively induced both diabetes and frailty in middle-aged mice. This model could serve as a valuable tool for evaluating interventions and translating findings to clinical practice, potentially shedding light on the complex relationship between diabetes and frailty in humans.

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褪黑激素改善db/db mice第二型糖尿病小鼠模型糖尿病視網膜病變經活化PINK1線粒體自噬作用

Melatonin Ameliorates Diabetic Retinopathy via PINK1-Dependent Activation of Mitophagy in db/db mice

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過去許多研究已證實，視網膜色素上皮（RPE）細胞中的炎症、氧化壓力、細胞凋亡和自噬與糖尿病視網膜病變（DR）有關。褪黑激素是一種負責晝夜節律的激素，已被證實具有抗炎作用，具有藥理特性並改善微循環障礙。然而，其對 DR 的有益作用和確切的機制仍有待闡明。在這項研究中，我們發現糖尿病小鼠的視網膜血管退化、視網膜厚度減少和視網膜功能受損導致新血管形成均通過口服褪黑激素（50 mg/kg）12 周顯著減弱。褪黑激素預處理還顯著抑制細胞凋亡，顯著抑制 VEGF 和 SDF1a 表達，顯著增加 PEDF 表達並顯著抑制初代細胞培養人類視網膜色素細胞 (HRPE) 受到 N-羧甲基賴氨酸 (CML)(糖基化終端代謝產物)的氧化壓力和發炎反應和糖尿病小鼠的視網膜中。此外，褪黑激素處理增加了 Phospho-PINK1 (Ser228) Phospho-Parkin (Ser65) 的含量，增加了 LC3-II/LC3-I 比率，但對 CML 誘導的 RPE 細胞中 p62/SQSTM1 的僅有輕微部分影響在糖尿病小鼠的視網膜中。此外，褪黑激素給藥增強了 RPE 細胞中 GFP-LC3 puncta 和 MitoTracker 的共定位。重要的是，轉染質體 ovPINK1 的過表達阻斷 CML 造成視網膜色素上皮（RPE）細胞損傷反應。綜合實驗發現，這些現象證實褪黑激素通過 PINK1 依賴性放大線粒體自噬來預防 DR。

本研究深入描述了糖尿病視網膜病變 (DR) 模型小鼠在不同疾病應激狀態下存在的糖尿病視網膜微血管生理異常，並提供了理解糖尿病患者執行功能改善的線粒體自噬細胞機制的關鍵。高血糖下的視網膜病變衍生出糖基化終產物與褪黑激素關鍵功能的藥物。

關鍵詞: 糖尿病視網膜病變；線粒體自噬；PINK1 蛋白；褪黑激素

Emerging evidence has demonstrated indicated that inflammation, oxidative stress, apoptosis, and autophagy in retinal pigment epithelial (RPE) cells are involved in diabetic retinopathy (DR). Melatonin, a hormone responsible for circadian rhythm, has been shown to possess anti-inflammatory effects, possesses pharmacological properties and improve microcirculatory disorders. Nevertheless, its beneficial effects on DR and the precise mechanism remain to be elucidated. In this study, we found retinal vascular degeneration, reduced retinal thickness, and impaired retinal function in diabetes mice result in neovascularization were all dramatically attenuated by oral treatment with Melatonin (50 mg/kg) for 12 weeks. Melatonin pretreatment also significantly inhibited apoptosis, markedly

suppressed the VEGF and SDF1a expression, markedly increased PEDF expression and markedly inhibited oxidative stress and inflammation in primary human retinal pigment cells (HRPE) subjected to N -Carboxymethyllysine (CML), an advanced glycation end products (AGEs) and in the retinas of diabetes mice. Furthermore, Melatonin pre-treatment upregulated the level of Phospho-PINK1 (Ser228) Phospho-Parkin (Ser65), increased the LC3-II/LC3-I ratio, and but slightly effect the level of p62/SQSTM1 in RPE cells induced by CML and in the retinas of diabetes mice. Moreover, Melatonin administration enhanced the co-localization of GFP-LC3 puncta and MitoTracker in RPE cells. Importantly, overexpression of PINK1 blocked the damaged effects of CML. In conclusion, these phenomena suggested that Melatonin prevented DR via PINK1-dependent magnify of mitophagy.

This study provides an in-depth description of the diabetic retinal microvascular physiological abnormalities present in different disease stress states in diabetic retinopathy (DR) model mice and provides the keys for understanding the cellular mechanisms in mitophagy underlying the improved executive function observed in people with diabetic retinopathy under hyperglycemia derive advanced glycation end products with medication of Melatonin crucial function.

Keywords：diabetic retinopathy; mitophagy; PINK1; Melatonin, AhR

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PAX3在台灣膠質瘤細胞複製壓力誘導的cGAS-STING途徑活化和抗藥中的關係探討

The role of PAX3 in cGAS-STING pathway activation and drug resistance induced by replication stress in Taiwanese glioma cells

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膠質瘤是中樞神經系統最常見的腫瘤，具有高度的惡性和侵襲性。儘管目前有許多治療方法，但膠質瘤患者的預後仍然很差。近年來，研究發現膠質瘤細胞中的複製壓力可能與其抗藥性和侵襲性有關。本研究旨在探討膠質瘤細胞中的複製壓力與化療藥物抗藥性之間的關係，以及複製壓力如何影響膠質瘤細胞的發炎反應和免疫反應。本研究使用 U87 膠質瘤細胞株和 HEK293 正常細胞株進行研究。首先，我們使用化學藥物 Hydroxyurea (HU) 誘導細胞中的複製壓力，並檢測細胞中的微核和 γH2AX 複製壓力的指標。然後，我們使用 RT-qPCR 檢測細胞中發炎反應相關基因 IL-6 和免疫反應相關基因 IFN-β的表現量。最後，我們收集 U87 細胞株的外泌體，並將其處理 HEK293 細胞株，觀察外泌體對 HEK293 細胞株的發炎反應和免疫反應的影響。U87 膠質瘤細胞株和 HEK293 正常細胞株在基礎的微核水平和 HU 誘導的微核水平上沒有顯著差異。外源性 PAX3 能夠降低 HU 和 5-Fluorouracil (5-FU)誘導的複製壓力。HU 誘導 HEK293 細胞株的發炎反應下降，而誘導 U87 膠質瘤細胞株的發炎反應上升。HU 誘導 HEK293 細胞株的免疫反應上升，而 U87 膠質瘤細胞株則測量不到免疫反應。U87 膠質瘤細胞株的外泌體能夠降低 HEK293 細胞株的發炎反應，而促進 HEK293 細胞株的免疫反應。本研究表明，膠質瘤細胞中的複製壓力可能與其化療藥物抗藥性有關。此外，複製壓力還可能影響膠質瘤細胞的發炎反應和免疫反應。這些發現可能為膠質瘤的治療提供新的思路。

關鍵詞：膠質母細胞瘤，發炎反應， 複製壓力，基因組不穩定性，抗藥性，免疫反應，外泌體，PAX3

Glioblastoma is the most common primary brain tumor in adults and is characterized by high malignancy and invasiveness. Despite multimodal treatment, the prognosis of patients with glioblastoma remains poor. Recent studies have shown that replication stress, a condition that occurs when DNA replication is perturbed, may be involved in the development and progression of glioblastoma. In this study, we used the U87 glioblastoma cell line and the HEK293 normal cell line to investigate the relationship between replication stress and

chemotherapeutic drug resistance in glioblastoma cells. We also explored how replication stress affects the inflammatory response and immune response of glioblastoma cells. U87 glioblastoma cells and HEK293 normal cells did not differ significantly in their basal levels of replication stress, as measured by micronuclei and γH2AX foci. Exogenous PAX3, a transcription factor known to regulate DNA replication, was able to reduce replication stress induced by HU and 5-fluorouracil (5-FU). HU treatment led to a decrease in the inflammatory response in HEK293 cells, but an increase in the inflammatory response in U87 glioblastoma cells. HU treatment led to an increase in the immune response in HEK293 cells, but no immune response was detected in U87 glioblastoma cells. Exosomes from U87 glioblastoma cells were able to reduce the inflammatory response in HEK293 cells but promote the immune response in HEK293 cells. Our findings suggest that replication stress in glioblastoma cells may be associated with chemotherapeutic drug resistance. Additionally, replication stress may also affect the inflammatory response and immune response of glioblastoma cells. These findings may provide new avenues for the treatment of glioblastoma.

Keywords：glioma, inflammatory responses, replication stress, genomic stability, Chemoresistence, immune responses, exosome, PAX3

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以小鼠模型探討臍帶間質幹細胞對紅斑性狼瘡的免疫調節作用

Investigation of Immunomodulary effect of umbilical mesenchymal stem cell therapy on systemic lupus erythematous using a murine model

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系統性紅斑狼瘡 (SLE) 是一種慢性多系統自體免疫疾病，目前用來治療 SLE 的藥物，包括類固醇、免疫抑制劑及生物製劑等，其對於不同類型的紅斑性狼瘡在使用上仍有限制，療效有限且仍然會增加感染的風險。之前藉由實驗動物模型的研究發現，人類臍帶間質幹細胞可以針對 SLE 做免疫調節。自 2007 年以來，已經陸續有些研究利用異體間質幹細胞來治療嚴重且對傳統治療效果不佳的 SLE 病患。整體而言，病患耐受度良好，相當安全且 5 年的疾病緩解率可達到 34%，5 年存活率可達 84%。因此，異體間質幹細胞治療是非常有希望可(UC-MSC) 以用來治療頑治型的 SLE 病患。本研究利用訊聯生技公司提供的人類臍帶間質幹細胞 針對誘導 SLE 小鼠進行治療。實驗結果顯示，UC-MSC 治療在第 7 週後顯著降低 SLE 小鼠血清中的 anti-dsDNA 自體抗體水平，且在第 15 週和第 26 週繼續維持這種抑制效果。此外，UC-MSC 治療後未對 SLE 小鼠的血尿素氮水平產生影響，表明其並不引起對腎功能的不良反應。進一步對 T 細胞分析揭示，UC-MSC 治療對 SLE 小鼠 T 細胞免疫反應產生調節作用，特別是減少 Treg 和 Th17 細胞，有助於緩解免疫系統的異常活化。總體而言，本研究強調 UC-MSC 治療作為 SLE 治療的潛在選擇，其對自體抗體生成、腎功能以及 T 細胞免疫反應的調節效果為進一步深入研究提供了基礎。此試驗將可作為未來進行人體試驗之臨床前動物試驗。

關鍵詞: 系統性紅斑狼瘡、臍帶間質幹細胞，小鼠

Systemic lupus erythematosus (SLE) is a chronic multi-systemic autoimmune disease. Current medications used to treat SLE, including corticosteroid, immunosuppressants and biologics, are still limited to treat various subtypes of SLE, having limited effect and still increasing the risk of infection. Prior animal studies have shown that human umbilical cord mesenchymal stem cells (UC-MSC) can have an immune-modulatory effect on SLE. Since 2007, several studies have used allogenic UC-MSC to treat SLE patients who are refractory to conventional therapies. Overall, patients tolerated UC-MSC therapy well, with good safety profiles and a clinical remission rate up to 34% and a 5-year survival rate up to 84%. Therefore, UC-MSC therapy is very promising to treat patients with difficult-to-treat SLE. The study will use human UC-MSC provided by BIONET Therapeutics Corp. (訊聯生技) to treat inducted lupus mice. Results revealed that UC-MSC treatment significantly reduced the levels of anti-dsDNA autoantibodies in SLE mouse serum after 7 weeks, and this inhibitory effect persisted at weeks 15 and 26. Additionally, UC-MSC treatment did not impact the blood urea

nitrogen levels in SLE mice, indicating no significant adverse effects on kidney function. Further analysis of T cells demonstrated that UC-MSC treatment exerted a regulatory effect on the T cell immune response in SLE mice, particularly reducing the percentages of Treg and Th17 cells, contributing to alleviating abnormal immune system activation. In conclusion, this study underscores the potential of UC-MSC therapy as a viable option for treating SLE, showcasing its regulatory effects on autoantibody generation, kidney function, and T cell immune response. These findings provide a foundation for further in-depth research, offering valuable insights for future clinical applications and the treatment of refractory SLE patients. This experiment serves as a preclinical animal trial for future human trials.

Keywords：systemic lupus erythematosus, umbilical cord mesenchymal stem cell, mice

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建立以D-galactose誘導老化動物模式並考量各器官組織Akr1a1之表現

Establishing an animal model of aging induced by D-galactose and considering the expression of Akr1a1 in various organs and tissues

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D-半乳糖誘導老化動物模式已經被使用於抗老化的研究中，經 D-半乳糖注射的動物陸續出現認知功能障礙、神經退行性病變、生育力降低、免疫反應降低、氧化壓力增加、勃起功能障礙、肝臟和心臟粒線體功能失調、以及引起皮膚彈性蛋白減少而引起的老化。我們使用 ICT 小鼠，飼養至 8 到 16 週大，經由腹腔內注射 0,4,8 g/kg D-galactose 約 8~28 週，欲觀察體重、跑步速度、下肢拉力等表現型；目前發現我們發現只要以 D 半乳糖給予的 ICT 小鼠，追蹤久了體重都會減輕。在給予 D 半乳糖後第 20 週，小鼠前肢力量沒有差異性，但小鼠走路持久力似乎是減退。考量各組織器官表現，以腎臟組織，發現 D-galactose 給予劑量越高，AKR1A1 與 PKM2 基因表現量有正向性越高的情形；腦部組織 AKR1A1 與 PKM2 基因表現量沒有一致性；肝臟組織，發現 D-galactose 給予劑量越高，AKR1A1 與 PKM2 基因表現量似乎呈現反向相關；脾臟組織 AKR1A1 與 PKM2 基因表現量也沒有特別的相關性;心臟組織，發現 D-galactose 給予劑量越高，AKR1A1 與 PKM2 基因表現量也沒有特別的相關性或呈反向相關。目前，我們預計先建立此 D-半乳糖誘發之老化動物的雛型，再進一步生理或病理機轉知探討。

關鍵詞: 誘導型老化動物模式、D-半乳糖、腎臟

D-galactose-induced aging animal models have been used in anti-aging research. Animals injected with D-galactose have been successively developed as models of cognitive dysfunction, neurodegeneration, reduced fertility, reduced immune response, increased oxidative stress, erectile dysfunction, mitochondrial dysfunction in the liver and heart, and age-related loss of skin elastin. We use ICT mice, raise them until they are 8 to 16 weeks old, and inject 0, 4, 8 g/kg D-galactose intraperitoneally for about 8 to 28 weeks to observe phenotypes such as body weight, running speed, and lower limb pulling strength. Currently, we have found as long as ICT mice were given D-galactose, they would lose weight over a long period of time. At 20 weeks after administration of D-galactose, there was no difference in the strength of the forelimbs of the mice, but the walking endurance of the mice seemed to be reduced. Considering the performance of each tissue and organ, for kidney tissue, it was found that the higher the dose of D-galactose, the higher the positive correlation between AKR1A1 and PKM2 gene expression; there was no consistency in the expression of AKR1A1 and PKM2 genes in brain tissue. In liver tissues, it was found that the higher the dose of D-galactose, the expression levels of AKR1A1 and PKM2 genes seemed to be inversely

correlated. There was no special correlation between AKR1A1 and PKM2 gene expression in spleen tissue. In heart tissues, it was found that the higher the dose of D-galactose, the expression levels of AKR1A1 and PKM2 were inversely related. There is no special correlation or inverse correlation between AKR1A1 and PKM2 gene expression. At present, we plan to establish the prototype of this D-galactose-induced aging animal first, and then further explore the physiological or pathological mechanisms.

Keywords：induced aging animal models, D-galactose, kidney.

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乳腺密度組織特徵識別：IVIM-MR 成像中使用深度神經網絡與信號強度衰減曲線進行分析

Breast tissue signature recognition: Using hyperspectral imaging techniques and signal intensity decay curves in IVIM-MR imaging

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乳癌是近年衛福部公佈的女性十大死因之一，而乳房緻密度的高低和乳癌的發生率有著高度的相關性. 我們將調查不同乳房類型中腺體和脂肪組織之間的差異，並將分析了乳房腫瘤與乳房緻密度的關係。我們將引入了高光譜處理來分析不同 b 值的 DW 成像。乳房類型的分類在實務上都以醫生的個人主觀意識去進行，本研究希望可以透過數值量化乳房內的腺體及脂肪的參數，提供較為客觀的分類基準。

乳房磁振造影技術(Magnetic Resonance Imaging, MRI)，不僅提供較高對比的影像，可用於影像分析，也不需考慮輻射的問題。遙測影像使用高光譜技術對於地質檢測的概念，可以用於 MRI 之特性產生不同 b 值的影像，本研究欲使用高光譜影像處理技術於體素內不同調水分子運動磁共振影像(Intravoxel Incoherent Motion, IVIM)，使用傳統影像演算法(Fuzzy C-means, FCM)與深度神經網路(Deep Neural Networks, DNN)，對健康的乳房做腺體與脂肪的分類，藉由不同 b 值間訊號的變化程度與定量分析參數，觀察乳房組織的數值，藉此看出腺體、脂肪的不同。

本研究欲使用 MATLAB 進行開發，透過 FCM 對乳房的腺體及脂肪進行分類，再收集各個個案的分類結果來訓練 DNN。藉由信號衰減圖，觀察不同的乳房型態，曲線的位置變化情況，最後，透過量化各類型乳房的外顯擴散係數(Apparent Diffusion Coefficient, ADC)、不同 b 值加權影像後之信號衰減程度(Slope)、純擴散係數(pure diffusion coefficient, D)、血液灌注係數(perfusion coefficient, D*)及灌注因子(perfusion fraction, PF)等參數進行統計分析，希望未來可以讓醫生透過量化後的數據進行臨床上的診斷。

關鍵詞：磁振造影影像、高光譜影像、體素內不同調水分子運動，深度神經網路

Breast cancer is one of the top ten causes of death in women announced by the Ministry of Health and Welfare in recent years, and the level of breast density is highly correlated with the incidence of breast cancer. We will investigate the differences between glandular and fat tissue in different breast types and analyze the relationship between breast tumor and breast density was also invistigated. We will introduce hyperspectral imaging processing techniques to analyze DW imaging for different b values. The classification of the breast type basically depends on the doctors. In this research, we will quantify the parameters of glands and fat in the breast and provide an objective standard.

Magnetic resonance imaging (MRI) not only offers the higher contrast images, but it also has no need to consider about radiation. The telemetry images use hyperspectral techniques in the concept of geological detection, it can be used for images of different b values. This research will use hyperspectral image processing technique on intravoxel incoherent motion (IVIM); we will use traditional image processing algorithm Fuzzy C-means (FCM) and deep neural networks (DNN) to classify glands and fat. We want observe the differences between glands and fat by the change between different b values and the quantitative analysis.

We will develop the algorithms in MATLAB in this research. By using FCM to classify glands and fat, we will collect the results from several cases and train the DNN by this data. We will observe the position change of the curve of different types of breasts through the degree of signal variation between different b values. Finally, calculating apparent diffusion coefficient (ADC), the slope of signal variation between different b values, the diffusion of tissue water molecules (D), blood perfusion (D*) and perfusion fraction (PF) for statistical analysis. We hope that we can offer a standard for the doctors to diagnosis in the future.

Keywords：Magnetic Resonance Imaging (MRI), Hyperspectral Image (HSI), Intravoxel incoherent motion (IVIM), Deep Neural Networks (DNN)

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探討光滑念珠菌Phd1及Sok2轉錄因子於黏附性調控之角色

Characterize the roles of Phd1 and Sok2 transcription factors in adherence of *Candida glabrata*

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真菌感染目前為全球重要的公共衛生問題其造成的死亡數超過每年 1 百萬人的死亡約與瘧疾或結核病死亡的人數相當。念珠菌病為常見真菌感染而主要由白色念珠菌及光滑念珠菌等病源菌所引起。光滑念珠菌為人體共生酵母菌，在人體免疫力低下或黏膜組織受損時會造成侵襲性念珠菌感染。此菌株對唑類抗真菌藥劑與氧化壓力有耐受性及強烈的表面黏附性導致生物膜形成造成臨床上治療的困難。過去釀酒酵母菌的研究中得知，真菌黏附性由 cAMP/PKA 訊號傳遞路徑的下游轉錄因子 Flo8、Phd1 及 Sok2 所調控。在白色念珠菌中，Flo8 及 Efg1 (Phd1 的同源蛋白) 可調控型態轉換、黏附性及毒性，然而相關蛋白在光滑念珠菌中尚未被研究。此研究發現光滑念珠菌的 Phd1 及 Sok2 蛋白在侵襲、生物膜形成及壓力反應上面扮演著不同角色。但只有 CgPhd1 可以誘導釀酒酵母菌的侵襲作用而 CgSok2 及 CgFlo8 則無法，且這三個蛋白質無法啟動黏附素 Flo11 的轉錄。總之，CgPhd1 及 CgSok2 在光滑念珠菌中調控黏附性及壓力反應等功能。

Fungal infections are emerging problems worldwide and cause annually more than one million deaths as malaria and tuberculosis. Candidiasis is a common fungal infection and is caused by *Candida albicans*, *Candida glabrata* and other *Candida* species as fungal pathogens. C. *glabrata* is a commensal on our body and can cause invasive candidiasis when the hosts are immunocompromised or the mucosal tissues are damaged. The virulent traits of this yeast include tolerance to azole antifungal drugs and oxidative stresses, and highly adherence to different surfaces for biofilm formation that lead to difficulty in treatments. In *Saccharomyces cerevisiae*, the fungal adherence is regulated by cyclic AMP protein kinase A signaling pathway and downstream transcriptional factors Flo8, Phd1 and Sok2. In addition, Flo8 and Efg1, a homologue of Phd1, also control morphogenesis, adherence and virulence in C. *albicans*; however, these proteins have not been characterized in C. *glabrata*. In this study, we explored the roles of Phd1 and Sok2 in agar invasion, biofilm formation and stress responses of C. *glabrata*. Interestingly, only CgPhd1 induces agar invasion but not CgFlo8 or CgSok2 in the S. *cerevisiae* background. Furthermore, none of these three transcription factors induced FLO11 expression in S. *cerevisiae.* In conclusion, CgPhd1 and CgSok2 regulate adherence and stress response in C. *glabrata*.

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小檗鹼誘發對紓癌特具抗性之腎癌細胞凋亡之訊遞機制

The signaling network for apoptosis induction of berberine on sunitinib-resistant renal cell carcinoma cells

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腎細胞癌約佔所有惡性腫瘤中的 2-3%，其罹病率逐年攀升中其中轉移性腎細胞癌佔所有腎細胞癌病例中的 25-30%，且臨床預後極差，因大多數病人常因為對於藥物產生抗藥性而導致化療失敗。紓癌特(Sunitinib)為轉移性腎細胞癌治療上最常使用的藥物之一，但卻因為經常有抗藥性之產生而導致一開始的有效控制之努力付諸流水。因此，基於上述理由，我們想要以腎細胞癌細胞(786-O)出發，先行建立一典型具有紓癌特抗藥性的腎細胞癌細胞株(Sun-R-786O)，再針對此細胞株來搜尋可以殺這種抗藥細胞株的藥物，並對其抗癌效果與胞內機制等等做一全面性的評估。我們已經由 786-O 細胞培養階段處理藥物(SUN)後建立了紓癌特抗藥性的腎細胞癌細胞株(Sun-R-786O)，並發現一個過去被發現可以抗癌的藥物---小檗鹼(berberine)不僅可以降低腎細胞癌之細胞活性，更對於所建立出之 Sun-R-786O 細胞株亦具有降低其細胞活性之效力。此外，小檗鹼可以增強 Sun-R-786O 細胞株中活化態的 caspase-3 和-9 蛋白的表現，並降低 UBN2，Bcl-2 和 Bcl-xL 的表達。本研究將有助於提供對於紓癌特等藥物使用後產生抗藥性或不良副作用的病患，在臨床治療上給予另一種藥物之臨床應用，兼具有學術與臨床之多重價值。

Renal cell carcinoma (RCC) accounts for approximately 2–3% of all malignant tumors, and its prevalence is rising. Metastatic RCC accounts for 25–30% of all RCC cases, and has an exceedingly poor prognosis.The resistance to anticancer drugs is the main cause of chemotherapy failure. Sunitinib (SUN) is a based antineoplastic agent and although it is effective in initially, the tumor cells eventually develop a drug-resistant ability during the course of therapy. Thus in this study, we are going to establish a Sunitinib-resistant RCC cancer cell (Sun-R-786O) and use it as a platform to search for the feasible anticancer drug for this Sun-R-786Ocell.In this project,our results showed that berberineis capablein suppressing the Sun-R-786O cell viability, inducing the cell apoptosis and increased sub-G1 cell induction. In addition, berberinecan expression of active form caspase-3 & -9 and decreased the expression of UBN2, Bcl-2 and Bcl-xL on Sun-R-786O cells. The study may successfully provide a drug screening platform and solution for Sunitinib-resistant RCC cancer patients.

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製備含微胞藥物之自修復抗菌水凝膠及其應用

Preparation of self-healing antibacterial hydrogel containing microcellular drugs and its application

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於本研究中，我們透過奈米纖維素的添加來製備 P(AA-co-NVP)雙網絡奈米複合水凝膠，由於纖維素的存量豐碩，並具有質量輕、可再生及奈米級的纖維等特性，且奈米級纖維素混摻能增益其熱性質、機械強度等優點，因此奈米纖維素在研究上獲得越來越多的關注。我們首先使用 TEMPO 氧化劑透過 TEMPO 氧化法來製備 TEMPO 氧化奈米纖維素(TEMPO-Oxidized Cellulose Nanofiber, TOCN)，接著透過單體本身的特性與不同的交聯鍵結使水凝膠賦予不同的功能。

第一部份我們透過丙烯酸(Acrylic acid, AA) 和 N- 乙烯基吡咯烷酮(NVP) 和 TEMPO 氧化奈米纖維素(TOCN)，製備出 P(AA-co-NVP)雙網絡奈米複合水凝膠，透過導入雙網絡的結構可以使水凝膠整體的性質提升，像是網絡結構的均一性或是機械性值等，且使用一鍋法的製程不僅簡單且快速，可提升製程上的效率與優勢，此外由於此水凝膠為全物理交聯，作用力間具有可逆且可自主解離和重組的特性，因此會有自修復的特性，並且透過陽離子與低 pH 值高分子的導入，使水凝膠具有抗菌效果，此種方便的製程並保有優良的機械性質、自修復特性和抗菌功能的材料，將對於材料開發方面極具潛在的應用優勢。

第二部份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。

接著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。

關鍵詞：奈米複合水凝膠、自修復特性、抗菌材料、薑黃素、藥物釋放

In this study, we prepared P(AA-co-NVP) double network nanohybrid hydrogels by composite TEMPO-Oxidized Cellulose Nanofiber. Due to the abundant stock of cellulose and the characteristics of light weight, renewable and nanoscale fibers, and with nanofiber mix in can increase the thermal properties, mechanical strength and other advantages, Therefore,

nanofiber has received more and more attention in research. we used the oxidant TEMPO to prepare TEMPO-Oxidized Cellulose Nanofiber (TOCN) by TEMPO oxidation method, and then through the characteristics of the monomer itself and different cross- linking bonds, the hydrogels will with different functions.

In the first part of this study, we prepared P(AA-co-NVP) nanohybrid hydrogels by Acrylic acid (AA) and N-vinylpyrrolidone (NVP) and TOCN. Double network can improve the overall properties of the hydrogels such as the uniformity of the network structure or the mechanical properties. The one pot method is not only simple and fast, but also improves the efficiency and advantages of the process. In addition, because the hydrogels is all physically cross-linked, the forces are reversible so the hydrogels will has self-healing properties. and through the cations and low pH polymers, the hydrogels has antibacterial effects. This convenient process and the materials with excellent mechanical properties, self-healing properties and antibacterial functions will let the hydrogels has great potential application for material development.

In the second part of this study, 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.

Next, 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.

Keywords：Nanohybrid hydrogels, Self-healing , Antibacterial, Curcumin, Drug release

榮靜計畫

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分析腦幹的變形指數作為預測聽神經鞘瘤加馬刀治療預後的分析

Analysis of deformity index in vital structure as the basis to predict outcome in large acoustic tumor after gamma knife radiosurgery

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背景：顯微外科手術是治療大型聽神經鞘瘤的主要方法，但立體定位放射手術的效益仍存在爭議。用加馬刀治療的大型神經鞘瘤，容易出現短暫的腫瘤擴張或腫瘤周圍水腫的不良副作用。本研究的目的是利用自動體積分析軟件來量化腦幹變形程度和腫瘤特徵，以預測加馬刀治療大型聽神經鞘瘤的預後及併發症。

材料和方法：2003 年至 2020 年間，有43個大型聽神經鞘瘤的患者（其腫瘤體積 > 8 c.c.）接受加馬刀治療，邊緣劑量為 10-12 Gy，這些患者擁有清晰可分析的 MRI 和詳細的病歷進可行分析。使用加馬刀治療時的所有 MRI序列和放射學特徵為每個病例進行參數分析。體積測量包括腫瘤體積（TV）、腦幹體積（BSV）、小腦體積（CerV）、囊性體積（CV）、水腫體積（EV）和第四腦室體積（VV），使用第22版Materialise Mimics(一種基於醫學 3D 圖像的工程軟件)。在最後一次收集到的MRI所計算的腫瘤體積被定義為最終的腫瘤體積，以計算腫瘤縮小的比率。腦幹的變形指數主要測量CV/TV、TV/BSA、TV/CerV、TV/BAS+CerV、TV+EV/BSA+CerV的比率。腫瘤側緣到中心線的距離和第四腦室體積是測量腦幹壓迫的其他變量。

結果評估：平均腫瘤體積為 13.7±6.3 cc，GKRS 後的平均追蹤時間為 86.7±65.3 個月。26 名 (66.7%) 患者觀察到良好的臨床結果，而 13 名 (33.3%) 患者治療失敗。患者患有腫瘤體積小、生命結構畸形指數低[(TV/(BSV+CerV)和(TV+EV)/(BSV+CerV)]以及腫瘤與中心線距離長的患者，術後更有可能獲得良好的臨床結果。 GKRS顯著的預後與腫瘤縮小率（<50%）相關的數值分別為CV、CV/TV、TV/CerV、（TV+EV）/（BSV+CerV）以及腫瘤到中心線的距離。在 cox 回歸中，良好的臨床結果與 Charlson 合併症指數和耳蝸劑量相關（均 $p<0.05$）。在多變量分析中，腫瘤消退與 CV/TV 比率高度相關（$p<0.001$）。

建議：腦幹畸形率可能是評估臨床和腫瘤消退結果的有用指標。臨床結果是多因素的，腫瘤消退與囊性成分的比例高度相關。

關鍵詞：聽神經鞘瘤、加馬刀放射手術、腦幹畸形、Charlson 合併症指數

Background：Microsurgery remains the mainstay of treatment for large vestibular schwannomas (VS), but the beneficial effect by radiosurgery is still debated. Large schwannoma treatment treated by gamma knife (GKRS) mostly predispose to unwanted

adverse effect of transient tumor expansion or peri-tumoral edema. The aim of this study was to utilize automatically volumetric analysis software to quantify the degree of deformity of brain stem and characteristics of tumor to predict the long-term outcome in patients with large VS after GKRS

Material and Method：Between 2003 and 2020, there were 43 patients with large VS (volume > 8 c.c.) undergoing GKRS with margin dose of 10-12 Gy with available MRI and medical record for analysis. All pretreatment MRI sequence were retrieved to assess the radiological characteristics and to conduct volumetric analysis for each case. The volumetric measurement, including the tumor volume (TV), brainstem volume (BSV), cerebellum volume (CerV), cystic volume (CV), edema volume (EV), and 4th ventricle volume (VV) was performed using the 22nd version of Materialise Mimics, a medical 3D image-based engineering software. The measurement of tumor volume at the last follow up defined as the final tumor volume was measured to calculate the ratio of tumor shrinkage. The parameters of CV/TV, TV/BSA, TV/CerV, TV/BAS+CerV, and TV+EV/BSA+CerV were measured to calculate the brainstem distortion index. Distance of lateral border of tumor to central line and 4th VV were other variables to measure the brain stem compression.

Result：Their mean tumor volume was 13.7±6.3 cc, and their mean follow-up after GKRS was 86.7±65.3 months. Favorable clinical outcome was observed in 26 (66.7%) patients, while 13 (33.3%) patients had treatment failure. Patients with small tumor volumes, low vital structure deformity indice [(TV/(BSV+CerV) and (TV+EV)/(BSV+CerV)], and long distance of tumor to the central line were more likely to have favorable clinical outcome after GKRS. Significant prognostic value was with tumor shrinkage ratio (<50%) were CV, CV/TV, TV/CerV, (TV+EV)/(BSV+CerV), and the distance of tumor to the central line. In cox regression, favorable clinical outcome was correlated with the Charlson comorbidity index and cochlear dosage (both $p<0.05$). In multivariant analysis, tumor regression was highly correlated with the CV/TV ratio ($p<0.001$).

Recommendation：The brainstem deformity ratio is likely a useful index to assess the clinical and tumor regression outcomes. Clinical outcomes are multifactorial and the tumor regression was highly correlated with the ratio of cystic components.

Keywords：acoustic tumor, gamma knife radiosurgery, brain stem deformity, Charlson co-morbidity index

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超高壓加工技術生產之米蛋白胜肽對改善糖尿病性心臟病機制之探討

Development of brown rice peptide by using high-pressure processing and its ameliorative potential against diabetic cardiomyopathy: insight into physicochemical properties and oxido-inflammatory factors

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米中的穀類蛋白，含有相當豐富的必須胺基酸，若能開發為保健原料，將可大幅提升其利用價值。米蛋白在半高溫糖化的步驟後，蛋白質分子間形成大量的雙硫鍵，使蛋白質分子交聯形成網狀結構，不利於蛋白質的溶解，因此限制米蛋白的應用範圍，因此若能克服米蛋白溶解度的問題,將可大幅增加碎米的附加價值。與傳統加工處理法比較，高壓處理後的食品能保持較好的風味與營養價值，與傳統的熱加工技術相比，高壓加工技術於常溫下操作,可免除升溫及後續冷卻過程能量的消耗,且因食品已是包裝的形態，不會與加工機具直接接觸，可避免殺菌後二次汙染的情況發生。由於看好忙碌的現代人追求快速、方便的訴求，進而開發米胜肽飲品，預期在未來市場佔有一席之地。

近年來植物蛋白為健康食品之趨勢，作為改善相關病症之營養獲得相當多學者的關注，目前市面上已經有很多關於大豆蛋白、豌豆蛋白等研究，而米蛋白因為其低敏的特性被視為重要的植物蛋白之一，近幾年對於肌少症的疾病重視，補充蛋白質飲食或開發強化添加蛋白質之食品逐漸受到重視，相關產品開發也越來越多，而此研究目的是希望透過處理將米蛋白轉變為更小分子的胜肽，以便能更好的應用於產品上。本次研究使用分為四組來進行比較，分別為未經處理的米蛋白對照組樣品A，經過酵素處理的樣品B，經過高壓加工技術(High pressure processing, HPP)處理的樣品C，以及酵素與高壓處理組合的樣品D。後續進行物理特性分析(色澤及外觀)、保水能力測試、水溶性分析、化學特性如胺基酸組成及含量、支鏈胺基酸含量、蛋白質含量、胜肽含量、巰基及二硫鍵含量分析。結果顯示，儘管酵素水解和 HPP 處理會影響米蛋白的外觀色澤，但蛋白質含量 (3120.31 ± 42.15)、支鏈胺基酸 (BCAA) 含量 (15.12 ± 1.03)、胜肽含量 (31.25 ± 0.55) 及胺基酸組成則顯著增加。此外，酵素水解和 HPP 處理有效地克服了米蛋白溶解度和保水能力之問題。 通過酵素水解和 HPP 處理生產的米蛋白表現出更高的自由基清除活性和氧自由基吸收能力。本研究通過使用酵素水解和 HPP 處理生產的米蛋白水解物顯示出在營養保健品行業中用作功能性食品成分的潛力。本研究通過酵素水解(Alcalase、papain、bromelain、Flavourzyme®)結合高壓加工技術處理(25 ℃ 下 400 MPa 15 分鐘)分離的米胜肽，顯示出在營養保健品行業中用作功能性食品成分的潛力。

Rice protein is a suitable alternative protein source for dairy protein in infant formulas on account of its unique nutrition and hypoallergenicity. Rice protein was isolated through enzymatic hydrolysis (Alcalase, papain, bromelain, Flavourzyme®) in combination with

high-pressure processing (HPP) (400 MPa for 15 min at 25 ℃) to enhance its functional properties and broaden its food processing applications. The results showed that even though enzymatic hydrolysis and HPP treatment affected the color of the resulting rice protein, the protein content (3120.31±42.15), branched chain amino acid (BCAA) content (15.12±1.03), peptide content (31.25±0.55), and amino acid composition of the rice protein were significantly increased. Moreover, the combined enzymatic and HPP treatment effectively overcame the problem of limited solubility and water-holding capacity. Rice protein produced through enzymatic and HPP treatment exhibited a higher free radical scavenging activity and oxygen radical absorbance capacity. The rice protein hydrolysate produced through enzymatic hydrolysis and HPP treatment showed the potential for use as an ingredient for functional foods in the nutraceutical industry.

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早產兒出生周齡與建立腸道菌相之關係性分析

Relationship between birth age and establishment of gut microbiota in preterm infants

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在前期計畫本研究團隊於嬰兒出生後第一個月內，每週收集一次糞便以 16S rDNA 定序分析新生兒腸道菌相。結果顯示早產兒和足月兒的腸道菌相存在顯著差異（p=0.0001），消化能力較佳之早產兒其腸道菌相較趨向於足月兒，包括有較豐富之消化相關細菌，此外糖和氨基酸代謝相關之酵素具較高的基因表現量。因此，前期研究結果顯示，消化系統和腸道菌相的成熟延遲是造成早產兒消化能力不足的主要原因本計畫擬接續前期研究，進一步探討早產兒出生周齡(或體重)與建立腸道菌相之關係性。本年度在臺中榮民總醫院兒童醫學中心收納早產兒 27 名(懷孕週數於 30　34 周，出生體重小於等於 1500 公克，每一周數各 5 名)。分別於新生兒一周齡至一月齡每周收集一次糞便，交與靜宜大學進行 DNA 抽取及 16S rDNA 定序。最後根據 16S rDNA 定序結果與已知之資料庫比對分析菌相。雖然結果顯示由於出生第一周同組間的差異過大，以致遮蔽組間(不同周齡)的差異，但比較第一周與第二周或第四周、第二周與第四周、第三周與第四周仍具顯著性差異。出生四周內菌種豐富度雖未增加，益生菌中之乳酸菌而第二周增加，在第四周雙叉桿菌量最高而腸桿菌科量最低；顯示健康菌叢逐漸建立。

In the previous project, the research team collected fecal samples once a week within the first month after birth of infants and analyzed the neonatal intestinal flora by 16S rDNA sequencing. The results showed that there were significant differences in the intestinal flora between preterm and full-term infants (p=0.0001). Preterm infants with better digestive ability had intestinal flora closer to full-term infants, including more abundant digestive-related bacteria. In addition, enzymes related to sugar and amino acid metabolism had higher gene expression levels. Therefore, the previous research results showed that the delay in the maturation of the digestive system and intestinal flora is the main cause of insufficient digestive ability in preterm infants. This project intends to continue the previous research and further explore the relationship between the gestational age (or weight) of preterm infants and the establishment of intestinal flora. This year, 27 preterm infants (gestational age 30-34 weeks, birth weight less than or equal to 1500 grams, 5 for each week) were enrolled in the Children's Medical Center of Taichung Veterans General Hospital. Fecal samples were collected once a week from one week to one month of age and sent to Providence University for DNA extraction and 16S rDNA sequencing. Finally, the flora was analyzed by comparing the 16S rDNA sequencing results with the known database. Although the results showed that the intra-group differences in the first week of birth were too large to mask the inter-group

(different age) differences, there were still significant differences between the first and second or fourth weeks, the second and fourth weeks, and the third and fourth weeks. The richness of bacterial species did not increase within four weeks of birth, but the lactobacilli in probiotics increased in the second week, and the bifidobacteria reached the highest level in the fourth week and the Enterobacteriaceae reached the lowest level; indicating that healthy flora gradually established.

TCVGH-PU1128104

開發基於手機 APP 之職業性肌肉骨骼傷害檢測系統

Development of occupational musculoskeletal disorders evaluation system based on mobile APP

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為了協助人因專家對 KIM-LHC 風險評估的判斷，本計畫開發了手機版 KIM-LHC 評估系統 APP，以快速產生肌肉骨骼傷害(MSD)的風險結果與建議。系統中我們設計了一系列使用者介面，讓使用者可自行輸入工作資訊。針對經常產生誤判的身體姿勢評級，我們使用 MoveNet 深度模型找出人體關節座標並計算肩、腰、膝關節等角度。最後，透過時序分析演算法評估每個動作的姿勢評級。在實驗部分，我們進行三次不同強度與頻率的工作行為測試。實驗結果證實，本研究所開發的 APP 不僅能立即產生風險評估結果與建議，同時與專業的人因專家所判斷的結果一致。更重要的是，整個過程僅透過一部手機即可完成，無需將資料上傳至雲端來進行運算。

In order to assist human factor experts in making judgments on the risk assessment of KIM-LHC, this work develops a mobile version of the KIM-LHC assessment system to quickly generate risk values and recommendations for musculoskeletal disorders (MSD). In the work, a series of user interfaces are designed to allow users to input various work information by themselves. For body posture evaluations that often lead to inaccurate judgements, we use the MoveNet deep model to generate human joint coordinates and calculate shoulder, waist, and knee joints angles. Finally, the timing analysis algorithm is used to find the posture rating corresponding to each action. In the experimental part, we conducted three tests of working behaviour with different intensities and frequencies. Experimental results show that the APP developed in this work is not only able to immediately generate risk value results and provide appropriate suggestions, but also has the same accuracy as human factors experts. In addition, the entire process is completed with a single mobile phone and there is no need to upload data to the cloud for calculation.

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COVID-19 急性感染後徵候群回溯性預測模型建立

An Approach on Retrospective Predictive Modeling of Post-COVID-19 Syndrome

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新冠肺炎綜合症候群（Post-COVID-19 Syndrome）又稱為長新冠（Long Covid），長新冠患者所帶來的後續效應、所付出的社會成本，也可能比我們想像的更為深遠，需要投入更多的資源關注。面對長新冠，許多問題都還需擁有更多分析資料，才能制定相應的政策。

雖然 2022 年 2 月衛福部開設了過百個新冠肺炎康復者整合門診，但相關有系統的研究與資料分析仍然缺乏。目前本院已收治相當數量的長新冠患者，在本計畫完成相關檢查記錄與長新冠診斷結果資料整理與串接，同時，我們也利用整理後的模型進行長新冠預測機器學習模型建立，並透過資料驗證模型準確性，初步結果在幾種機器學習模型下，均具有相當高的準確性。

關鍵詞：COVID-19 急性感染後徵候群、機器學習、分類、預測

Post-COVID-19 Syndrome, also known as Long Covid, has more far-reaching consequences and social costs than we thought and requires more resources. Many issues need more analysis before policies can be formulated.

The Ministry of Health and Welfare opened over 100 integrated outpatient clinics for recovered patients in February 2022. At present, our hospital has admitted a considerable number of patients with long new crowns. In this project, we have completed the data collation and concatenation of the relevant examination records and the diagnostic results of long new crowns, and at the same time, we have also conducted the long new crowns prediction machine-learning model establishment using the collated model and verified the model accuracy with the data, and the preliminary results have fairly high accuracy under several machine-learning models.

Translated with www.DeepL.com/Translator (free version)

Keywords：Post-COVID-19 Syndrome, Machine Learning, Classification, Prediction

榮聯計畫

TCVGH-NUU1128901

調節局部表面電漿共振之電漿子金屬/石墨烯奈米材料於人體體液中電化學生物分子感測平台

Plasmonic metal-graphene nanomaterials-based tunable local surface plasmon resonance (LSPR) for electrochemical biomolecules sensing platform in human fluids

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3D Ni 其多孔結構利於提升材料比表面積，而石墨烯具有良好的電化學性能，金奈米粒子在針對過氧化氫則具有良好的氧化還原的能力，將以上材料開發三維多孔鎳與石墨烯複合材料並結合金奈米粒子開發 3D NiAu@Graphene。透過 3D NiAu@Graphene 結合光電化學開發非酵素過氧化氫感測器，藉由掃描式電子顯微鏡(Scanning electron microscope, SEM)以及穿透式電子顯微鏡(Transmission electron microscope, TEM)觀察材料表面形貌，並藉由 X 光光電子能譜學(X-ray photoelectron spectroscopy, XPS)進行元素分析，利用光電化學觀察材料針對過氧化氫氧化還原的能力，並進一步進行定量分析，證實其材料之可行性。在實際應用中，此次計畫開發之 3D NiAu@Graphene 電極在真實人類血清中 H2O2 的檢測中展現優異回收率，結果證實 3D Ni@Graphene 在非酵素 H2O2 光電化學感測具廣泛的應用前景。

關鍵詞: 非酵素過氧化氫光電化學感測器、3D NiAu@Graphene、人體血清

In this study, integration of Au and graphene in 3D nickel template (3D NiAu@Graphene) was synthesized by a one-step electrochemical method for non-enzymatic H2O2 photoelectrochemical sensing. The physicochemical properties of 3D NiAu@Graphene were characterized by scanning electron microscopy (SEM), transmission electron microscope (TEM), Raman spectroscopy, and X-ray photoelectron spectroscopy (XPS). The obtained 3D NiAu@Graphene own its synergistic effects from Au, 2D graphene architecture, and highly porous 3D nickel template can exposes more electroactive sites and tune electronic structure that facilitates the electron/ion transfer during the photoelectrochemical processes to get sufficient electrochemical responses for the detection of H2O2. In practical application, 3D NiAu@Graphene electrode prepared in this work shows good recovery for the determination of H2O2 in human serum. These results demonstrate that 3D Ni@Graphene have promising applications in the fabrication of non-enzymatic H2O2 photoelectrochemical sensing.

Keywords: non-enzymatic H2O2 photoelectrochemical sensing, 3D NiAu@Graphene, human serum

TCVGH-NUU1128902

開發以慣量量測單元為主之中風後病患步態數據採擷分析系統

Development of inertial measurement unit-based post-stroke gait data acquisition and analysis system

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在台灣中風是十大死因的第五位，腦中風通常會遺留下不同程度的神經功能障礙，嚴重影響生活品質。在中風治療的過程中，復健是治療最重要的環節之一，而步態的恢復一直被認定為最主要的復健目標，評量步態品質是透過研究步態模式和特定的步態特徵。隨著科技的進步發展，今日小型、輕型的慣量量測單元(Inertial Measurement Unit, IMU）穿戴式感測器，正在迅速革新研究環境中的步態評估，提供在實驗室外和自然環境（診所、運動場等）中收集數據的研究潛力，並有極大潛力被納入常規臨床測量中。本計畫基於前一期計畫的成果基礎上，在可採集下肢復健數位化資料之穿戴式裝置上開發步態數據採擷分析系統，設計機器學習演算法及計算步態參數，推演設計適合步態表現指標，與醫師的觀察性步態分析結果做比對，分析二者間的關聯性。這計畫對於臨床上步態的客觀評估，將是一件很有意義的事。

關鍵詞：中風後步態評估，慣量量測單元，機器學習

Stroke is the fifth leading cause of death in Taiwan. A stroke usually leaves various degrees of neurological dysfunction, seriously affecting the quality of life. In the process of stroke treatment, rehabilitation is one of the most critical aspects of treatment, and gait recovery has consistently been recognized as the primary goal of healing. Gait quality is assessed by studying gait patterns and specific gait characteristics. With the advancement of technology, today's small, lightweight Inertial Measurement Unit (IMU) wearable sensors are rapidly revolutionizing the gait assessment in research environments, offering the potential to collect data in outdoor and natural environments (clinics, sports arenas, etc.). They may be incorporated into routine clinical practice. Based on the results of the previous project, we developed a gait data acquisition and analysis system based on wearable devices that can collect digital gait data, designed a machine learning algorithm, computed gait parameters, and deduced a suitable gait performance index. This indicator will be compared with the physician's observational gait analysis results, and the correlation between these two will be analyzed. This program could bring objective measurement for gait analysis in clinical settings, which is meaningful for clinical workers.

Keywords : post-stroke gait assessment, inertial measurement unit, machine learning

TCVGH-NUU1128903

將槲皮素用於預防與減緩視網膜色素上皮細胞發炎反應之研究

The Study of Quercetin in Prevention and Reducing Inflammatory Response of Retinal Pigment Epithelium Cell

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據統計全球人口在 2020 年約有 1.956 億人因老化而罹患了黃斑部病變(age-related macular degeneration，AMD)，此疾病之全球醫藥市場規模初估在 2021 年約有 74.7 億美元之市場價值。近年來因人口老化速度增加，老年性黃斑部病變的患者數量預估將會持續不斷的增加到 2030 年，因此預計未來 20 年老年性黃斑部病變的醫藥市場價值將會持續增加到 590 億美元。老化、基因變異、營養失衡與富含自由基的環境都可能是致病因子，導致視網膜色素上皮細胞(retinal pigment epithelium，RPE)退化，再進一步即可有可能導致老年性黃斑部病變與失明。該種病症臨床上目前尚無有效可行的治療方法。槲皮素，也稱為 3,3',4',5,7-五羥基黃酮，是一種天然類黃酮，且存在於許多水果、蔬菜、葉子、種子和穀物中。因此，在本研究中，我們評估了槲皮素用於預防與治療發炎的視網膜色素上皮細胞 RPE 之效果，實驗上分別設計了前處理和後處理兩種實驗流程來評估槲皮素的預防保護和治療發炎的效果。實驗結果以 WST-1 試劑檢測細胞活性、即時定量 PCR 技術檢測 mRNA。我們發現用於 RPE 培養的槲皮素濃度不應高於 100 μM。實驗中以 1 到 100 μM 濃度的槲皮素培養 RPE 細胞時，可發現細胞活性無顯著差異，但若以 1000 μM 的槲皮素濃度培養，則細胞活性的 OD 值下降。另外當細胞以槲皮素進行預先培養處理時，我們發現當濃度低於 100 μM 時，無論細胞隨後是否受到 IL-1β或 HNE 刺激，都具有相當的保護作用。但若將細胞先以促發炎因子 IL-1β或 HNE 刺激後再加入槲皮素，就只有 1 和 10 μM 組的表現良好。更重要的是，我們發現加入 1 ng/mL 的 IL-1β可誘導 RPE 細胞合成 IL-1β和 IL-6 發炎蛋白的 mRNA。然而，若在進行細胞培養時，無論是先或後加入 10 μM 的槲皮素，均可有效降低 RPE 細胞的發炎反應。因此，我們建議在未來的應用上可添加 10 μM 槲皮素用於視網膜細胞的抗發炎治療上。以上的結果將有助於我們進行後續的體內動物實驗進行驗證，我們希望這項研究能為 AMD 患者提供一種新的治療方法或選擇。

關鍵詞：老年性黃斑部病變、槲皮素、視網膜色素上皮細胞、抗發炎

It is approximate that in 2020 around 195.6 million people would suffer from age-related macular degeneration (AMD), and the global AMD market was valued at USD 7.47 billion in 2021. Due to the growing elderly population, the patient number will continuous increased to 2030. As a result, the cost of AMD is predicted to increase to $59 billion over the next 20 years. Ageing, genetic disorder, nutrition unbalance, and free radical-rich environment are risk factors related to AMD, and lead to retinal pigment epithelium (RPE) degeneration, then lead to AMD and blindness. Clinically, there is no effective and feasible method for the treatment of AMD. Quercetin, also named 3,3´,4´,5,7-pentahydroxyflavone, is a natural flavonoid present in many fruits, vegetables, leaves, seeds, and grains. Thus, in this study, we evaluate

quercetin in prevention and reducing inflammatory response of retinal pigment epithelium cell. We design pre-treatment and post-treatment experiment to evaluate both the protection and treatment effect of quercetin. Cell viability was checked by WST-1 reagent, mRNA was evaluated by real-time PCR. We found quercetin concentration used for RPE cultivation should not be higher than 100 μm. Results showed that there was no significant difference in RPE cell viability in 1, 10 and 100 μM groups, but the OD value was decreased significantly in 1000 μM group. When cells were pre-treatment with quercetin, we found there is a protective effect at the concentration lower than 100 μM, regardless of whether the cells were subsequently stimulated by IL-1β or HNE proinflammatory factor. But when the cells first received IL-1β or HNE, only groups 1 and 10 μM performed well. Besides, we also found that with the addition of 1 ng/mL IL-1β could induce RPE cells synthesize IL-1β and IL-6 mRNA. However, with the treatment of 10 μM quercetin, no matter in pre-treatment or post-treatment condition, RPE cells inflammatory response decreased. Thus, we suggested 10 μM quercetin addition could be the optimal concentration for anti-inflammation treatment. These results would assist us do further in vivo animal study, and we hope these studies could provide a new method/choice for AMD patient.

Keywords: age-related macular degeneration, quercetin, retinal pigment epithelium, anti-inflammation

TCVGH-NUU1128904

抗氧化與抗發炎之模型建立與驗證評估

Model Establishment and Validation Evaluation of Anti-oxidation and Anti-inflammation

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氧化作用常是引起發炎反應的重要原因，然而文獻上關於抗氧化劑之抗氧化與抗發炎關聯性並未清楚釐清。本計畫探討抗氧化劑在常見自由基之抗氧化與抗發炎的關係，計畫中選用 myricetin、eriodictyol、luteolin、kaempferol、apigenin、quercetin 六種常見之抗氧化標準品，分析標準品在清除 DPPH 自由基、ABTS 自由基、超氧自由基、羥基自由基之抗氧化能力，以及在細胞發炎模式下，對 TNF-α、IL-1β、IL-6、NO 等發炎指標之抗發炎能力，再以多變數分析法迴歸分析抗氧化與抗發炎之量化數學關係，進而建立以抗氧化能力預估抗發炎能力之模型。未來有機會能以簡易的抗氧化分析實驗進行繁雜之細胞抗發炎能力預估，加速抗發炎篩選平台之評估速度。

Oxidation is often an important cause of inflammatory response, but the relationship between anti-oxidization and anti-inflammation of antioxidants has not been clarified in the literatures. This project explored the relationship between anti-oxidization and anti-inflammation in common free radicals. In the project, myricetin, eriodictyol, luteolin, kaempferol, apigenin, and quercetin were used as antioxidant standards. The antioxidant capacity in scavenging DPPH free radicals, ABTS free radicals, superoxide free radicals, and hydroxyl free radicals, and the anti-inflammatory capacity of TNF-α, IL-1β, IL-6, and NO inflammatory indicators in the mode of cell inflammation were analyzed by multivariate analysis. The quantitative mathematical relationship between anti-oxidization and anti-inflammatory was analyzed by regression analysis, and then a model for predicting anti-inflammatory ability based on antioxidant capacity was established. In the future, simple antioxidant experiments can be applied to estimate the anti-inflammatory ability in complex cell experiments to accelerate the evaluation of anti-inflammatory screening platforms.

榮陽計畫

TCVGH-YM1120101

利用單細胞RNA定序及基因分型來研究急性骨髓細胞性白血病產生化學抗性之機制

To study the mechanism of chemoresistance in acute myeloid leukemia through single-cell RNA sequencing and genotyping

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在這項前瞻性研究中，我們調查了新診斷的急性骨髓性白血病（AML）患者在接受「7+3」誘導化療方案前，針對化療抗藥性的潛在因素。我們招募了20名AML患者，治療後將其分為15名完全緩解（CR）和5名非CR (non-CR)患者。利用單細胞RNA定序（scRNA-seq）來探討白血病幹細胞（LSCs）在化療抗藥性中的作用。將診斷時的骨髓單核細胞進行了全面分析，以識別LSCs及其遺傳特徵。我們發現顯示，非CR患者的AML細胞中，在造血過程中未成熟細胞群體顯著增加。值得注意的是，我們觀察到CR組中的LSCs表現的髓過氧化物酶（MPO）和甲狀腺釋放激素（TRH）mRNA，相較於非CR組顯著提高。這種差異表達經獨立患者隊列驗證後得到進一步證實。此外， MPO和TRH表現量較高的患者，無復發生存率和總生存率都明顯改善。總結而言，我們的研究確定了LSCs中MPO和TRH表達作為AML化療敏感性的潛在生物標記。這些結果表明，基於這些生物標記對患者進行分層，為新診斷的AML案例量身定制誘導治療，可能增強治療效果並改善患者預後，是一條有希望的途徑。

關鍵詞：急性骨髓系性白血病、化療抗藥性、白血病幹細胞、單細胞RNA定序、完全緩解

In this prospective study, we investigated the underlying factors contributing to chemoresistance in de novo Acute Myeloid Leukemia (AML) patients undergoing the '7+3' induction chemotherapy regimen. A cohort of 20 consecutive patients was enrolled and categorized post-treatment into complete remission (CR) and non-CR groups, comprising 15 and 5 patients, respectively. The primary objective was to elucidate the role of leukemia stem cells (LSCs) in mediating chemoresistance, utilizing single-cell RNA sequencing (scRNA-seq). We conducted a comprehensive analysis of bone marrow mononuclear cells at diagnosis to identify LSCs and their genetic profiles. Our findings revealed a marked increase in immature cell populations during hematopoiesis within the AML cells of non-CR patients. Significantly, we observed elevated expressions of Myeloperoxidase (MPO) and Thyrotropin-releasing hormone (TRH) in the LSCs of the CR group, compared to their non-CR counterparts. This differential expression was further corroborated by validation in independent patient cohorts. Moreover, the clinical relevance of these findings was underscored by the observation that

patients exhibiting higher MPO and TRH levels demonstrated notably improved relapse-free and overall survival rates. In conclusion, our study identifies MPO and TRH expressions in LSCs as potential biomarkers for chemosensitivity in AML. These results suggest a promising avenue for stratifying patients based on these biomarkers to tailor induction therapy in newly diagnosed AML cases, potentially enhancing treatment efficacy and patient outcomes.

Keywords: Acute Myeloid Leukemia (AML), Chemoresistance, Leukemia Stem Cells (LSCs), Single-cell RNA sequencing (scRNA-seq), Complete Remission (CR)

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探討僵直性脊椎炎HLA-B*27以外之遺傳前置因子及風險評估

Investigate the genetic predispositions factors other than HLA-B*27 and risk assessment of ankylosing spondylitis

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【背景】

類風濕性關節炎是一種慢性發炎性的關節疾病，通常受侵犯的關節中，最常見也是最嚴重的是手部關節。疾病活動度評估工具，常見有綜合指標 DAS28，但僅以關節壓痛及腫漲、發炎指數、病患主觀評分來評估仍有相當的侷限性。而關節壓痛且病患主觀整體評分也可能受到合併纖維肌痛症而高估，這些因素都會影響疾病活動度 DAS28 的準確度。另外近年來也常用骨骼肌肉超音波來進行較客觀與科學化之評估，然而骨超本身是一個高度仰賴操作者的檢查，不同操作者的技術與判讀所造成的差異會影響診斷。且完成多處關節超音波掃描需要花費較長的時間，使骨骼肌肉超音波之使用受到限制。因此，開發一套更能貼近臨床醫療診斷輔助之智慧化工具，如此可提供臨床醫師進行客觀與科學化之診斷。

【目的】

本研究計畫預計評估在疾病活動期之類風濕性關節炎患者，再藥物調整前及調整後 84 天，針對腕部關節評估高光譜軟性豐度值之變化，並和超音波影像定量分析(Matlab Software 定量計算滑膜面積和 Power Doppler signals 面積)及臨床評估之疾病活動度(DAS28)等級變化做比較，評估高光譜軟性豐度值是否能反映出治療前後之發炎程度之差異。

【方法與材料】

本研究將用於分析類風濕性關節炎嚴重程度評估的高光譜技術主要有下列二個步驟：第一步，高光譜影像前處理，主要是取出感興趣分析區域。第二步使用軟性豐度計分器(Soft Abundance Scorer)輸出類風濕性關節炎之拍攝區域的豐度分數圖譜(Abundance Fraction Map)，作為最後輸出結果。並配合醫師臨床診察、及超音波檢查結果，進行後續類風濕性關節炎高光譜特徵差異性分析，及相關性分析。

【研究成果】

本研究對提出軟性豐度計分器法於評估類風濕性關節炎患者疾病等級做出了幾個主要的貢獻：1.本研究提出內部-軟性豐度計分器(Intra-Soft Abundance Scorer)法，來評估受試者本身在治療前和治療後的光譜差異性。2.本研究提出外部-軟性豐度計分器(Inter-Soft Abundance Scorer)法，來評估治療前和治療後，兩群體之間的光譜差異性。3.本研究提出的軟性豐度計分器的結果為軟決策，其豐度分數圖譜可以視覺化的觀察光譜差異性的變化，有助於臨床人員做視覺診斷。4.建立非侵入且非接觸性類風濕關節炎高光譜影像偵測之基礎，改善傳統檢驗方式，提供後續臨床應用技術之開發基礎。

關鍵詞：類風濕關節炎、高光譜成像軟性豐度計分器、豐度分數圖譜

Rheumatoid arthritis is a chronic inflammatory joint disease. Among the joints affected, the wrist joint is usually the most common involved joint with the greatest severity. The composite index DAS28 is a commonly used disease activity assessment tool. However, disease activity assessment may be inaccurate by evaluating the severity of joint tenderness, swelling, inflammatory markers, and subjective severity scores. The joint tenderness and the patient's overall subjective score may also be overestimated by the concomitant fibromyalgia. These factors will affect the accuracy of the disease activity DAS28. In addition, in recent years, musculoskeletal ultrasound has been commonly used for more objective and scientific evaluation. However, musculoskeletal ultrasound is an examination that highly depends on the operator, and the differences caused by the techniques and interpretation of different operators will affect the diagnosis. Moreover, it takes a long time to complete the ultrasound scan of multiple joints, which limits the use of skeletal muscle ultrasound. Therefore, the development of an intelligent tool can provide clinicians with objective and scientific diagnosis is very important.

This project is to evaluate the patients with rheumatoid arthritis in the active stage of the disease, before and 84 days after the drug adjustment, the changes in the hyperspectral soft abundance value of the wrist joints will be evaluated, and ultrasound imaging will be used quantitative analysis (Matlab software quantitative calculation of synovial area and power Doppler signal area), and clinical evaluation of disease activity (DAS28) grade changes are compared to assess whether the hyperspectral soft abundance value can reflect the difference in the degree of inflammation before and after treatment.

We will develop a set of objective, fast and scientific hyperspectral algorithms to assess the degree of joint inflammation. Here we call this algorithm the Hyperspectral Imaging Soft Abundance Scorer (HISAS). The soft abundance image calculated by the hyperspectral detection system can be used to judge the degree of joint inflammation. This study will explore the wrists of patients with rheumatoid arthritis in the active disease stage before and after treatment escalation. We will assess whether there is any change in the value of Soft Abundance Scorer, and compare it with the results of Abundance Fraction Map and musculoskeletal ultrasonographic examination.

We hope this study will offer new efficient hyperspectral imaging processing methods with Intra-Soft Abundance Scorer and Inter-Soft Abundance Scorer for early diagnosis of different grades of rheumatoid arthritis diseases. Finally, it evaluates the feasibility of using hyperspectral imaging technology in the clinical application of rheumatoid arthritis.

Keywords : rheumatoid arthritis, Hyperspectral imaging soft abundance scorer, Abundance Fraction Map

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ABCG2 rs22311422基因多態性、生活型態因子與腎結石之相關性研究

The association study of ABCG2 rs2231142 variant, lifestyle , and nephrolithiasis

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背景：

國外全基因組關聯研究（genome-wide association studies，GWAS）針對了腎結石進行探討，研究顯示，腎結石與 ABCG2 rs2231142 的發病存在一定的遺傳關聯性，並與性別和種族相關，且受飲食、喝酒、肥胖等生活型態因素所影響。然而，目前針對本土 ABCG2 rs2231142 多態性與生活型態有關的風險因子間的交互作用造成之腎結石與後續慢性病之相關研究仍然闕如。因此，本研究之目的在釐清 ABCG2 rs2231142 與生活型態風險因子的交互作用所造成之影響，以及評估 ABCG2 rs2231142 與腎結石相關慢性疾病之風險。

目的：

1. 探討 ABCG2 rs2231142 變異與腎結石的關係。
2. 探討 ABCG2 rs2231142 生活型態風險因子的交互作用所造成之影響。

方法：

本研究將利用臺灣人體生物資料庫所提供之研究資料庫，進行病例對照研究，瞭解臺灣地區 ABCG2 rs2231142 與生活型態因子的交互作用和腎結石之間的關聯性。評估在不同年齡/性別階層中，ABCG2 rs2231142 多態性和腎結石之關聯性，以及建立 ABCG2 rs2231142 多態性與生活型態因子的預測模型。這些研究成果將有助於瞭解 ABCG2 rs2231142 基因與疾病風險之相關性，讓高風險族群可以在早期就透過改善生活習慣或飲食控制方式，降低疾病風險，達到個人化精準預防之目的。

結果：

本研究 ABCG2 rs2231142 的基因型頻率為 53%（T allele），共有 8,410 名參與者罹患腎結石，與 GG 基因型相比， TT(adjusted OR = 1.18，95%CI = 1.09－1.28）和 GT(adjusted OR = 1.12，95%CI = 1.06－1.18）更容易罹患腎結石，特別是在患有高尿酸血症的男性族群（p<0.001）。年齡較大、男性、高脂血症、高血壓、糖尿病、高尿酸血症、吸煙和體重過重是增加罹患腎結石風險。相反，規律運動可以預防罹患腎結石。

結論：

根據本研究顯示，ABCG2 基因變異是腎結石的一個重要風險，我們的結果提供了精準醫療的證據，並建議規律運動以預防腎結石。

關鍵詞：全基因組關聯研究、全表型體學關聯研究、腎結石、ABCG2 rs2231142 單核苷酸多態性

Background：

The uric acid stones is the third most common nephrolithiasis in less than10% attributed by the predisposing factors of persistently low urinary pH, hypovolemia (low urine volume), and hyperuricosuria. Significant predisposing factors leading to nephrolithiasis are classified into five categories as lifestyle, genetics, diet, environment and associated diseases. Previous genome-wide association studies (GWAS) have suggested an association between hyperuricemia and common dysfunctional variants in ATP-binding cassette, subfamily G, member 2 (ABCG2 rs2231142). However, the association between ABCG2 rs2231142 variants and nephrolithiasis, as well as their interactions with sex and lifestyle risk factors and subsequent chronic diseases is still unclear. Therefore, we will investigate whether the ABCG2 rs2231142 polymorphism are associated with risk of nephrolithiasis in a Taiwanese population.

Aims：

1.To investigate the association of ABCG2 rs2231142 variant and nephrolithiasis.

2.To investigate the interaction of ABCG2 rs2231142 variant and related predisposing factors contributes to the risk of nephrolithiasis.

Methods：

The case-control study will be conducted by using the Taiwan Biobank database to investigate whether the risk of nephrolithiasis was associated with ABCG2 rs2231142 variants which affected by lifestyle, diet, environment and associated clinical risk factors in different genders.

Results：

The frequency of rs2231142 T allele was 53%, and 8,410 participants had nephrolithiasis. The multivariable-adjusted OR (95% confidence interval) ofnephrolithiasis was 1.18 (1.09–1.28) and 1.12 (1.06–1.18) for TT and GT genotypes, respectively, compared with the GG genotype ($p<0.001$),specifically in the male population with hyperuricemia. Higher age, male sex,hyperlipidemia, hypertension, diabetes mellitus, hyperuricemia, smoking and overweight were independent risk factors for nephrolithiasis. In contrast, regular physical exercise is a protective factor against nephrolithiasis.

Conclusions：

ABCG2 genetic variation is a significant risk of nephrolithiasis, independent of serum uric acid levels. For rs2231142 T allele carriers, our result provides evidence for precision healthcare to tackle hyperuricemia, comorbidities, smoking, and overweight, and recommend regular physical exercise for the prevention of nephrolithiasis.

Keywords： genome-wide association studies, nephrolithiasis, ABCG2 rs2231142 single nucleotide polymorphism

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主動式與被動式短波紅外高光譜成像儀於糖尿病周邊神經病變偵測輔助診斷比較之研究

A comparative study of active and passive short-wave infrared hyperspectral imaging in the detection of diabetic peripheral neuropathy

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糖尿病周邊神經病變在相關慢性併發症中發生最早，盛行率高達30~50%，又與糖尿病截肢等嚴重的併發症相關。目前的檢查方式相對主觀量化困難，在新興傳染病疫情狀況下更形侷限。本研究團隊致力於開發短波紅外高光譜成像技術於糖尿病足之臨床輔助診斷工具，結果與電化學皮膚電導檢測(electrochemical skinconductance, ESC)高度負相關。成果取得設計專利，並發表第一篇利用900-1700nm短波紅外高光譜探討糖尿病周邊神經病變的論文。但此論文中仍有可以改善之處，如高光譜成像儀硬體之改良、及光譜差異性分析方法容易受到雜訊或樣本間的小變化干擾等問題。本研究主要目的是透過建立仿主動式高光譜成像儀7波段影像資料庫進行新的專家模型分析，並與過去蒐集的推掃式高光譜影像分析結果比較，以驗證主動式短波紅外LED高光譜成像儀於臨床應用之可行性。

本研究提出一項「核化最小平方正交次空間投影 (Kernel Least Square Orthogonal Subspace Projection, KLSOSP)」專家模型方法，它是第一次用於糖尿病足小神經病變高光譜影像之分析。此外也會收集受試者之心血管風險病史、糖尿病相關病史、基本身體檢查與臨床檢驗資料，如性別、年齡、糖尿病史、血液生化生理檢查、ABI (Ankle-Brachial Index)、及DN檢測（包含10公克單股纖維壓覺（Monofilament Testing）、電化學皮膚電導檢測 (electrochemical skin conductance, ESC)）等臨床數據。本計畫執行的分析結果，與過去被動推掃式短波紅外高光譜影像分析結果比較後，可以發現下列4點結論：

1.本研究提出利用核化最小平方正交次空間投影來改善光譜差異性分析容易受到雜訊或樣本間微小變化干擾造成分類誤差的問題，並從糖尿病足仿主動式短波紅外高光譜影像資料庫分析結果發現KLSOSP方法之ROC曲下面積為最高(0.885)，其準確率也是最高(0.824)；
2.本計畫透過上述專家模型驗證後，建置一台7波段之主動式短波紅外LED高光譜成像儀，可供臨床之收案，其硬體之體積可減少約40%，重量至少可減少50%以上。
3.主動式短波紅外LED高光譜成像儀之發光模式與被動推掃式高光譜成像儀之鹵素燈發光模式不同，可減少使用者或患者被燙傷之風險。
4.主動式短波紅外LED高光譜成像儀之拍照時間，因為只需拍7張波段影像，時間只需約20秒左右，與被動推掃式高光譜成像儀之拍攝時間約3分鐘相比，可節省9倍以上。

關鍵詞：主動式近紅外多光譜成像、糖尿病週邊神經病變、核化最小平方正交次空間投影、光譜差異性分析

Diabetic peripheral neuropathy (DPN) occurs early among chronic complications of diabetes, with a prevalence rate of 30-50%. It is also linked to severe complications like amputation. Current diagnostic methods are relatively subjective and difficult to quantify, a challenge exacerbated by the recent pandemic. Our research team has been dedicated to developing short-wave infrared (SWIR) hyperspectral imaging technology as a clinical diagnostic tool for diabetic foot. This technology shows a strong negative correlation with electrochemical skin conductance (ESC). The findings have resulted in a design patent and the first published paper using 900-1700nm SWIR hyperspectral imaging to study DPN.

However, the paper identified areas for improvement, such as enhancements to the hyperspectral imaging hardware and issues with spectral analysis methods, which are prone to noise and minor sample variations.

This study aims to establish a 7-band active SWIR LED hyperspectral imaging database for new expert model analysis and compare it with past pushbroom hyperspectral imaging results to validate the feasibility of the active SWIR hyperspectral imaging system for clinical use.

We propose a "Kernel Least Square Orthogonal Subspace Projection (KLSOSP)" expert model method, used for the first time in analyzing SWIR hyperspectral images of minor nerve changes in diabetic feet. The study also gathers data on cardiovascular risk, diabetes history, basic physical examinations, and clinical tests, including gender, age, diabetes history, blood biochemical tests, Ankle-Brachial Index (ABI), and DN tests (including 10g monofilament testing and ESC).

The analysis outcomes, compared with previous passive hyperspectral imaging results, reveal four main conclusions:

1. The proposed KLSOSP method improves spectral difference analysis, reducing classification errors caused by noise or minor sample variations, achieving the highest area under the ROC curve (0.885) and accuracy (0.824).
2. Following validation with the expert model, a new 7-band active SWIR LED hyperspectral imager has been developed, reducing the hardware size by about 40% and weight by more than 50%.
3. The active SWIR LED hyperspectral imager uses a different lighting mode from the halogen lamps of passive hyperspectral imagers, reducing the risk of burns to users or patients.
4. The photo-taking time with the active SWIR LED hyperspectral imager is about 20 seconds for 7 spectral images, saving over 9 times the time compared to the 3 minutes required by passive hyperspectral imagers.

Keywords: Active near-infrared multi-spectral imaging, diabetic peripheral neuropathy, Kernel Least Square Orthogonal Subspace Projection (KLSOSP), spectral difference analysis

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以磁振造影技術探究神經精神性狼瘡患者腦部膠淋巴系統功能

Evaluation of glymphatic system activity in neuropsychiatric systemic lupus erythematosus patients with normal structural brain

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神經精神性紅斑性狼瘡（Neuropsychiatric systemic lupus erythematosus NPSLE）影響神經系統並具有高死亡率。在一般傳統的腦部磁振造影像檢查中，約 50%的 NPSLE 患者具有正常的大腦巨觀結構，這導致疾病評估和治療困難且缺乏標準。先前的研究提出 NPSLE 自體抗體可能引起淋巴系統異常。在本次計畫中，擬針對這群在腦部磁振造影像中無明顯可偵測異常病徵的神經精神性紅斑性狼瘡病患進行膠淋巴系統成像的量化分析研究，旨在找到 NPSLE 的影像生物標記。

本研究包括 27 名 NPSLE 女性患者和 34 名年齡相匹配的女性參與者。參與者接受了三種認知評估：蒙特婁認知評估（Montreal Cognitive Assessment, MoCA）、簡易心智量表（Mini Mental Status Examination, MMSE）、額葉評估量表（Frontal Assessment Battery, FAB），以及腦部磁振造影。淋巴功能異常的影像指標包括：1) 評估大腦血管周邊空間(perivascular space, PVS)的擴大和其空間分佈等形態學分析。2) 量測大腦自由水(free water mapping, FW)的體積分數。3) 以擴散張量分析和大腦血管周邊之擴散係數(diffusion tensor image analysis along the perivascular space, DTI-ALPS)。大腦動脈供應圖譜用於確定淋巴異常的區域分佈。

在 NPSLE 組中，DTI-ALPS 顯著降低，而前腦動脈的中央豆狀核-紋狀體區域和中腦動脈的外側豆狀核-紋狀體區域的 FW 均值顯著升高。在 NPSLE 組的認知評估方面，PVS volume fraction 與所有評估呈負相關，而和全腦 DTI-ALPS 及 FW 值呈正相關。總結來說，NPSLE 患者表現出局部淋巴功能異常和廢物清除效率降低。認知評估的分析說明這些局部淋巴異常可能促成 NPSLE 相關的認知障礙。

Neuropsychiatric systemic lupus erythematosus (NPSLE) significantly impacts the nervous system and mortality rates. Despite the prevalence of normal brain macrostructure in approximately 50% of NPSLE patients according to clinical MRI protocols, this introduces challenges in disease assessment and treatment. Previous research has proposed that NPSLE autoantibodies may induce abnormalities in the glymphatic system. Our study utilized advanced MRI techniques to scrutinize glymphatic function, aiming to identify imaging biomarkers indicative of NPSLE.

Twenty-seven female NPSLE patients without abnormal WMH and 34 age-matched females were included in this study. Participants underwent three cognitive

assessments —MoCA, MMSE, and FAB — as well as an MRI scan. The image indicators of glymphatic dysfunction included: 1) enlargement of perivascular space (PVS); 2) free water (FW) mapping; and 3) diffusion tensor image analysis along the perivascular space (DTI-ALPS). The arterial atlas was applied to determine regional variations in glymphatic abnormalities.

In the NPSLE group, the FW mean values were significantly higher in the medial lenticulostriate of the anterior cerebral artery and the lateral lenticulostriate of the middle cerebral artery, while the DTI-ALPS reduced significantly. Regarding cognitive assessments in the NPSLE group, the PVS volume fraction showed a negative correlation with all assessments, whereas the global DTI-ALPS and FW values exhibited positive correlations. In summary, NPSLE patients presented localized glymphatic dysfunction and reduced efficiency in waste clearance. Cognitive assessments suggested that these localized glymphatic abnormalities may contribute to NPSLE-related cognitive impairment.

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褪黑激素改善鏈脲佐菌素誘導的第一型糖尿病小鼠模型糖尿病視網膜病變經活化PINK1的線粒體自噬作用

Melatonin Ameliorates Diabetic Retinopathy via PINK1-Dependent Activation of Mitophagy in Streptozotocin-Induced Diabetic Mouse Models

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過去許多研究已證實，視網膜色素上皮（RPE）細胞中的炎症、氧化壓力、細胞凋亡和自噬與糖尿 病視網膜病變（DR）有關。褪黑激素是一種負責晝夜節律的激素，已被證實具有抗炎作用，具有藥 理特性並改善微循環障礙。然而，其對 DR 的有益作用和確切的機制仍有待闡明。在這項研究中， 我們發現糖尿病小鼠的視網膜血管退化、視網膜厚度減少和視網膜功能受損導致新血管形成均通過 口服褪黑激素（50 mg/kg） 12 週顯著減弱。褪黑激素預處理還顯著抑制細胞凋亡，顯著抑制 VEGF 和 SDF1a 表達，顯著增加 PEDF 表達並顯著抑制初代細胞培養人類視網膜色素細胞 (HRPE) 受到 N-羧甲基賴氨酸 (CML)（糖基化終端代謝產物）的氧化壓力和發炎反應和糖尿病小鼠的視網膜中。 此外，褪黑激素處理增加了 Phospho-PINK1 (Ser228) Phospho-Parkin (Ser65) 的表達含量，也提升了 LC3- II/LC3-I 比率，但對 CML 誘導的 RPE 細胞中 p62/SQSTM1 的僅有輕微部分影響在第一型糖尿病 小鼠的視網膜中。此外，褪黑激素給藥增強了 RPE 細胞中 GFP-LC3 puncta 和 MitoTracker 的共定位。重要的是，轉染質體 ovPINK1 的過表達阻斷 CML 造成視網膜色素上皮（RPE）細胞損傷反應。綜合實驗研究結果發現，這些現象證實褪黑激素通過 PINK1 依賴性放大線粒體自噬來預防 DR。

關鍵詞：糖尿病視網膜病變； 線粒體自噬； PINK1 蛋白； 褪黑激素

Emerging evidence has demonstrated indicated that inflammation, oxidative stress, apoptosis, and autophagy in retinal pigment epithelial (RPE) cells are involved in diabetic retinopathy (DR). Melatonin, a hormone responsible for circadian rhythm, has been shown to possess anti-inflammatory effects, possesses pharmacological properties and improve microcirculatory disorders. Nevertheless, its beneficial effects on DR and the precise mechanism remain to be elucidated. In this study, we found retinal vascular degeneration, reduced retinal thickness, and impaired retinal function in diabetes mice result in neovascularization were all dramatically attenuated by oral treatment with Melatonin (50 mg/kg) for 12 weeks. Melatonin pretreatment also significantly inhibited cell permeability, increased TEER, markedly suppressed the VEGF and SDF1a expression, markedly increased PEDF expression and markedly inhibited oxidative stress and inflammation in primary human retinal pigment cells (HRPE) and ARPE-19 cells subjected to Nε-Carboxymethyllysine (CML), an advanced glycation end products (AGEs) and in the retinas of diabetes mice. Furthermore,

Melatonin pre-treatment upregulated the level of Phospho-PINK1 (Ser228) Phospho-Parkin (Ser65), increased the LC3-II/LC3-I ratio, and but slightly effect the level of p62/SQSTM1 in RPE cells induced by CML and in the retinas of diabetes mice. Moreover, Melatonin administration enhanced the co-localization of GFP-LC3 puncta and MitoTracker in RPE cells. Importantly, overexpression of PINK1 blocked the damaged effects of CML. In conclusion, these phenomena suggested that Melatonin prevented DR via PINK1- dependent magnify of mitophagy.

Keywords: diabetic retinopathy; mitophagy; PINK1; Melatonin

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NOTCH3 R544C基因變異者之功能性腦部MRI及腦白質病變相關因子研究

The study of factors associated with functional brain MRI and white matter hyperintensities in subjects with NOTCH3 R544C mutation

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本研究招募臺中榮總參加台灣精準醫療計畫中確認為帶有 *NOTCH3* R544C 突變的個案及沒有 *NOTCH3* R544C 突變的健康控制組受試者，收集受試者患者之腦部磁振造影影像數據後，進行大腦白質病變體積和擴散張量影像的分析。分析帶有突變和沒有突變受試者白質病變體積年齡的分布。比較兩組之間認知功能、白質病變體積和擴散張量影像分析數值的差異。根據此研究的結果中，依據年齡分布，使用 maximally selected rank and statistics 分析，*NOTCH3* R544C 基因變異之受試者白質病變增加的趨勢約在 48 歲左右開始，無基因變異者的白質病變在 30~70 歲的分布上並無明顯增加轉折點，且基因變異受試者認知功能已經有部分變差的現象，在 Fixel-based analysis 分析擴散張量影像的結果上發現 anterior and superior thalamic radiation, fronto-pontine tract, striato-fronto-orbital, and superior cerebellar peduncle 為影響最大的區域，之後的長期追蹤研究將分析白質病變增加的速度在不同年齡層的差異，和其與臨床症狀之間的相關性。

關鍵詞：體顯性腦動脈血管病變合併皮質下腦梗塞及腦白質病變、腦部核磁共振

This study recruited participants confirmed to have *NOTCH3* R544C mutations from the Taiwan Precision Medicine Initiative in Taichung Veterans General Hospital for cross-sectional analysis and long-term tracking. We collected clinical, genetic data and brain magnetic resonance imaging (MRI) images of all participants. Clinical data collection used structured clinical symptom questionnaires, neuropsychological test kits, and genetic data, and performed image analysis for white matter hyperintensities volume and diffusion tensor imaging (DTI). In this study, 63 participants carrying NOTCH3 R544C mutations and 37 healthy controls were analyzed. Our data showed the white matter hyperintensities increased after age of 48 years in NOTCH3 R544C mutation carriers. The cognitive function of NOTCH3 R544C mutation carriers was worse than the healthy controls in some neuropsychological tests. In addition, the fixel-based analysis demonstrated statistically significant differences in diffusion metrics between groups in anterior and superior thalamic radiation, fronto-pontine tract, striato-fronto-orbital tract, and superior cerebellar peduncle. Further studies about the rate of white matter hyperintensities increment in different age and its association with clinical symptoms will be investigated.

Keywords: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Brain MRI

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血栓病變動物模式保健功效探討

Health-promoting evaluation in rodent model of thrombotic diseases

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血栓併發症及凝血病變好發於新冠肺炎、敗血症、外傷患者，與患者高死亡率有關。此外，凝血活性上升也出現在肥胖及第二型糖尿病患者，與疾病後遺症有關。糖尿病是一種持續性代謝疾病，伴隨著脂質、碳水化合物、蛋白質代謝異常。肥胖族群屬於第二型糖尿病高風險好發對象。2019 年全世界 65 歲以上族群預估的糖尿病患者約一億一千一百萬。到 2045 年，預估數字上升到二億七千六百萬。在台灣，65 歲以上男性糖尿病流行率約 39.2%，女性約 40.6%。第二型糖尿病會導致急慢性器官傷害及併發症。肥胖及第二型糖尿病更是血栓形成的危害因子，容易導致靜脈血栓栓塞及動脈血栓症。除了是重要的能量代謝器官外，內臟脂肪組織更是促發炎因子及促凝血因子的表現釋出源頭。脂肪組織脂泌素中 leptin、resistin、visfatin 具有活化促凝血因子表現活性作用，adiponectin 則可干擾抑制促凝血因子表現活性作用。研究顯示，細胞衰老是脂肪組織異常的關鍵之一。脂肪組織的細胞衰老誘發促發炎細胞激素及脂泌素的不正常表現，導致胰島素抗性。移除衰老細胞，有助於緩解胰島素抗性及代謝異常。因此，細胞衰老是闡述第二型糖尿病慢性發炎、代謝異常、促血栓症等病變及治療的重要標的。為了著重在糖尿病併發症的病變機制及開發治療策略，本研究計畫係以高脂飲食誘導肥胖 C57BL/6 鼠配合低劑量 streptozotocin 的第二型糖尿病鼠模式來進行。Metformin 是臨床上治療第二型糖尿病的主要藥物，因此 metformin、植化素 baicalin、移除衰老細胞藥物 (dasatinib and quercetin) 將一併測試，進行比較分析。本年度計畫著重在脂肪組織角色探討，視實驗進度及結果，再擴展到其他調控標的的分析。糖尿病鼠呈現高體重、ALT、AST、total cholesterol、triglycerides、BUN。Metformin、baicalin、移除衰老細胞藥物，可改善 ALT、AST、BUN。帶是具有多樣性作用在體重、total cholesterol、triglycerides。糖尿病鼠出現高血糖、葡萄糖耐受異常、胰島素敏感異常。Metformin、baicalin、移除衰老細胞藥物，可改善葡萄糖代謝異常問題。糖尿病鼠有高 WBC 及 P-Selectin 濃度，但是血小板數量低下。Metformin、baicalin、移除衰老細胞藥物，可改善 WBC 及 P-Selectin 濃度變化，但是只有 baicalin 緩解血小板的低下。糖尿病鼠縮短出血時間，。Metformin、baicalin、移除衰老細胞藥物，可延長出血時間。關於分子路徑分析方面，皮下脂肪組織及附睪脂肪組織為分析標的。Western blotting 技術分析評估牽涉的分子。目前分析結果多樣，仍須進一步分析評估。實驗所收集的檢體組織仍會持續分析，已獲得更多的實驗結果。

關鍵詞：糖尿病；血栓；細胞衰老

Thrombotic complications and coagulopathy are frequently occurred in patients of COVID-19, sepsis, and trauma and associated with high mortality. Additionally, profound activation of the blood coagulation cascade is evident in patients with obesity and type 2 diabetic mellitus (DM) and contributes to disease sequelae. DM represents a persistent metabolic disease characterized by changes on the metabolism of fats, carbohydrates, and proteins. Particularly, obese populations are prone to the development of type 2 DM. The estimated number of people over 65 years of age with DM worldwide is 111 million in 2019 and will reach 276 million by 2045. In Taiwan, the prevalence of DM in people older than 65 years of age is 39.2% in men and 40.6 % in women. Type 2 DM causes not only acute but also chronic organ injury and an array of complications. Obesity and type 2 DM are risk factors for thrombosis and strongly associated with venous thromboembolism and arterial thrombosis. Beyond being vital organ for energy metabolism, visceral adipose tissues are important sources of pro-inflammatory and pro-coagulant factors. Furthermore, adipokines such as leptin, resistin, and visfatin have pro-thrombotic properties, while adiponectin displays anti-thrombotic effect. Evidence indicates that cellular senescence is a key component of adipose tissue dysfunction leading to aberrant expression of cytokines and adipokines, and insulin resistance. Removal of senescent cells improves metabolic abnormalities. Therefore, cellular senescence represents crucial target regarding type 2 DM-related inflammation, metabolic derangements, and pro-thrombotic transition pathogenesis and therapeutic treatment. To extend the study centered on diabetic complications and identification of therapeutic strategies, this study was investigated through a rodent model of type 2 DM, high-fat diet-fed obese C57BL/6 mice together with low dose of streptozotocin injection. DM mice at the end of study had increases in body weight, ALT, AST, total cholesterol, triglycerides, and BUN. Metformin, baicalin, and senolytic agent improved altered ALT, AST, and BUN, while had variable effects on body weight, total cholesterol, and triglycerides. DM mice developed hyperglycemia, glucose intolerance, and insulin insensitivity. Metformin, baicalin, and senolytic agent had improved effects on those alterations in DM mice. DM mice had increased WBC and P-Selectin content, while showed decreased platelet number. Metformin, baicalin, and senolytic agent alleviated the increases in WBC and P-Selectin content. However, only baicalin displayed alleviative effect on the reduction of platelet number. DM mice shortened the breeding time. Metformin, baicalin, and senolytic agent prolonged the breeding time when compared with DM mice control. To evaluate any changes in fat tissues, subcutaneous fat tissues and epididymal fat tissues were collected for analysis. Western blotting was applied for the evaluation and determination of intracellular signaling molecules involved. Although several biochemical and molecular evaluation had been performed, the detailed action mechanisms are still incomplete. Further analysis will be continued from those obtained tissue samples.

Keywords: Diabetes; Thrombosis; Senescence

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人工智慧準確判讀ICG影像定位淋巴管走向

Computer Vision-Assisted Lymphatic Vessels Detection in ICG Images

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淋巴靜脈吻合術（LVA）是治療淋巴水腫的常用且有效的手術，其中尋找淋巴水腫肢體的淋巴管走向是至關重要的一步。 對於輕度淋巴水腫患者，可以使用吲哚菁綠（ICG）影像來識別淋巴管。然而，對於嚴重肢體淋巴水腫患者，嚴重的淋巴回流阻塞可能會導致 ICG 影像上出現大量白點。通常透過在人體對稱的前提下，可用手動測量將正常肢體的淋巴管方向和位置投影到淋巴水腫肢體來解決，這導致前期手術的工作量很大。這為現代電腦視覺技術提供了絕佳的機會。在這項工作中，我們提出使用 U-Net 來獲得正常肢體的淋巴管分割，結合淋巴管的關鍵點和 Procrustes 分析來找到它們的對稱點，將翻轉的正常肢體的關鍵點鏡像到淋巴水腫影像，最後透過 Procrustes 變換將淋巴管分割映射到目標淋巴水腫影像。由於嚴重淋巴水腫的 ICG 影像難以識別，因此我們在實驗中使用輕度淋巴水腫的 ICG 影像，並專注於足部。分割、關鍵點偵測和 Procrustes 分析是我們的主要方法。淋巴管分割的準確度為 0.967。關鍵點偵測的物件關鍵點相似度為 9.46。用於 Procrustes 分析的歸一化 Procrustes 距離在 0.004 到 0.013 像素之間。 結合 Unity 平台和微軟 HoloLens 虛擬實境（VR）和擴增實境（AR）設備，將鏡像映射結果顯示在設備螢幕上。醫生可以同時看到淋巴管和患者腳部的預測位置。透過人工智慧和電腦影像處理方法來預測淋巴管的位置，不僅可以減少手術時間和感染風險，還可以讓醫生在手術過程中更專注於其他流程。

關鍵詞：淋巴管、淋巴管靜脈管吻合術、肢體淋巴水腫、淋巴管檢測、電腦視覺、機器學習和人工智慧。

Lymphatic venous anastomosis (LVA) is a common and effective surgery for the treatment of lymphedema, during which finding the directions of lymphatic vessels in an edema limb is a crucial step. For mild lymphedema patients, it is possible to identify lymphatic vessels with the assistance of indocyanine green (ICG) imaging. However, for severe lymphedema patients, the severe lymphatic obstructions may cause lots of white dots on ICG images. This is typically resolved by manually projecting the directions and positions of the lymphatic vessels from the normal limb to the lymphedema limb based on the premise of human body symmetry, leading to significant efforts for preceding operation. This poses a perfect opportunity for modern computer vision techniques. In this work, we propose to use attention U-Net to get the segmentation of lymphatic vessels of the normal limb, combine key points and Procrustes analysis for lymphatic vessel to find their mapping, mirror the key points of the flipped normal limb to the lymphedema image, and finally map the lymphatic vessels

segmentation to the target lymphedema image by Procrustes transformation. Because the ICG image of severe lymphedema is hard to recognize, we use the ICG image of mild lymphedema in our experiment and focus on feet. Segmentation, key-points detection and Procrustes analysis are main parts of our method. The accuracy is 0.967 for lymphatic vessel segmentation. The object key-point similarity is 9.46 for key-points detection. The normalized Procrustes distance is between 0.004 to 0.013 pixels for Procrustes analysis. Combining with Unity platform and Microsoft HoloLens, a virtual reality (VR) and augmented reality (AR) device and putting the mirror mapping result on the screen of device. The doctor can see the predictive location of lymphatic vessel and the feet of patient at the same time. By artificial intelligence and computer image processing method to predict the location of lymphatic vessel can not only reduce the operation time and the risk of infection, but also let doctors more focus at others processes during surgery.

Keywords : lymphatic vessels, lymphatic venous anastomosis (LVA), lymphedema of limbs, lymphatic vessels detection (LVD), computer vision, machine learning, and artificial intelligence.

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HLA基因及胺基酸變異與自體免疫疾病相關之探討

Association of HLA allele and amino acid variations with autoimmune diseases

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背景：
類風濕關節炎（RA）是一種自體免疫性疾病，其發病過程中腫瘤壞死因子（TNF）-α發揮著關鍵作用。多年來，許多抗 TNF-α生物制劑已經被開發並廣泛應用於 RA 治療。然而，儘管抗 TNF-α生物制劑的開發取得了成功，但約有三分之一的 RA 患者對此類療法無效。鑒於生物制劑療法所涉及的高成本，急需確定與藥物敏感性相關的遺傳標記。

目標：
本計畫旨在通過 HLA 基因座的深度序列分析，探討 HLA 基因變異與 TNF-α抑制劑對 RA 治療反應之間的關係，以及建立與評估治療反應相關的預測模型。

方法：
我們納入了 33 名接受阿達木單抗或依替諾膚注射治療的 RA 患者。對這些患者進行了針對 HLA 的深度序列分析，並識別了 HLA I 和 II 類基因內的單核苷酸變異（SNV）。然後，進行了關聯分析以研究這些 SNV 與歐洲風濕聯盟（EULAR）對 TNF-α抑制劑的治療反應之間的關係。最終，利用邏輯回歸計算了這些 SNV 的勝算比和 95%信心區間。從關聯分析中識別出了 12 個 p 值小於 0.05 的非同義 SNV，並根據連鎖不平衡分析進一步確定了其中的六個。

結果：
基於這些 SNV，我們建立了基於支持向量機（SVM）和隨機森林的預測模型，分別包含十二個和六個非同義 SNV。通過 ROC 分析，確定了這些模型的品質。

結論：
本研究表明，基於 NGS 的 HLA 序列分析可以識別與 TNF-α抑制劑治療反應的相關性，為未來 RA 精準醫學治療策略的應用提供了新的思路。

關鍵詞：類風濕關節炎，抗 TNF-alpha，依替諾膚注射，阿達木單抗，治療反應，人類白細胞抗原

Background:
Rheumatoid arthritis (RA) is an autoimmune disease in which tumor necrosis factor (TNF)-α plays a crucial role in its pathogenesis. Over the years, numerous anti-TNF-α biologics have been developed and widely used in the treatment of RA. However, despite the success in the development of these biologics, approximately one-third of RA patients do not respond to this

class of therapy. Given the high costs associated with biologics therapy, identifying genetic markers associated with drug susceptibility is an urgent need.

Objective:

This project aimed to explore the relationship between HLA gene variations and the response to TNF-α inhibitors in the treatment of RA through deep sequencing analysis of the HLA loci. Additionally, the project aimed to establish and evaluate predictive models for treatment response.

Methods:

Thirty-three RA patients treated with adalimumab or etanercept were enrolled in the study. Deep sequencing analysis targeting the HLA region was performed on these patients to identify single nucleotide variants (SNVs) within the HLA class I and class II genes. Subsequently, an association analysis was conducted to investigate the relationship between these SNVs and the European League Against Rheumatism (EULAR) responses to TNF-α inhibitors in RA patients. Odds ratios and corresponding 95% confidence intervals were calculated using logistic regression. Twelve non-synonymous SNVs with a p-value < 0.05 were identified from the association analysis, and six non-synonymous SNVs were further confirmed based on linkage disequilibrium analysis.

Results:

Based on these SNVs, predictive models were constructed using support vector machine (SVM) and random forest techniques, incorporating twelve and six non-synonymous SNVs, respectively. The quality of these models was determined through ROC analysis.

Conclusion:

This study demonstrates that NGS-based HLA sequencing can identify associations with TNF-α inhibitor treatment responses, providing insights for the future application of precision medicine in RA therapeutic strategies.

Keywords: rheumatoid arthritis, anti-TNF-alpha, etanercept, adalimumab, treatment response, human leukocyte antigen

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探討IL-4的葡萄糖代謝異常改善作用特性

Action mechanisms of IL-4-mediated improvement of glucose metabolic abnormalities

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肥胖會伴隨許多慢性及代謝異常疾病。嗜中性白血球的增生、浸潤、活化，也是肥胖相關慢性發炎反應的變化之一。肥胖可觀察到嗜中性白血球胞外網狀結構的形成，與胰島素抗性正相關，干擾抑制嗜中性白血球胞外網狀結構，可改善肥胖代謝異常及併發症。雖然已有許多研究顯示，嗜中性白血球胞外網狀結構在肥胖及非酒精性脂肪肝病的致病傷害角色，調控嗜中性白血球胞外網狀結構產生的特性，尚未有進一步探討。本研究計畫採用高脂飼料肥胖鼠非酒精性脂肪肝病動物模式,第一部份透過 Drp1 粒線體分裂抑制劑 Mdivi-1 為對象，分析粒線體異常的非酒精性脂肪肝病作用。同時與 IL-4 進行比較。IL-4、Mdivi-1 的介入、有效降低體重、肝臟組織重量、附睪脂肪重量變化。肥胖鼠組動物血液 ALT 及 AST 上升、禁食血糖上升、總膽固醇上升、三酸甘油脂上升、肝臟三酸甘油脂含量上升。IL-4、Mdivi-1，有效降低。IL-4、Mdivi-1，都可改善肥胖鼠組動物的肝臟組織病理異常、葡萄糖耐受性異常、胰島素敏感性低下、發炎細胞激素 IL-6 mRNA 表現、脂質過氧化物 MDA 含量、血液循環 Citrullinated Histone H3 及 dsDNA 含量。第二部份計畫進一步測試嗜中性白血球胞外網狀結構 PAD4 抑制劑 Cl-amidine、STING 抑制劑 C-176、Sirt1 活化劑 Resveratrol、HMGB1 抑制劑 Glycyrrhizic acid 的潛在功能角色。結果發現，Cl-amidine、C-176、Resveratrol、Glycyrrhizic acid 處理組，都可改善肥胖動物的葡萄糖耐受性異常、胰島素敏感性低下、血液總膽固醇上升。針對細胞內分子路徑變化，收集肝臟組織、腓腸肌組織、附睪脂肪組織蛋白質，藉由 Western blot 進行分析評估。分析對象包括：P-AMPK、HMGB1、P-IRS1、P-TBK1、TLR4、PAD4、P-STING、STING、P-IRF3、cGAS、PI3K p85、Neutrophil elastase、P-IR 、Glut4、RAGE、Sirt1、P-Akt。這些路徑分子的變化及角色，仍在持續測試。詳細的分子作用機制，仍需持續探討分析。本計畫與榮台聯大計畫同時進行，利用同一批實驗動物進行分析。

關鍵詞：肥胖；粒線體失能；糖尿病；嗜中性白血球胞外網狀結構

Obesity is a known risk factor for many chronic diseases and is associated with metabolic abnormality. Neutrophil proliferation, infiltration, and activation are changes of obesity-associated chronic inflammation. Neutrophil extracellular traps (NET) is revealed in obesity and contributes to insulin resistance and its suppression improves obesity-associated metabolic abnormalities and complications. Although there are many studies showing the

pathogenic effects of NET towards obesity and NAFLD, regulatory mechanisms underlying its establishment are largely unclear. In this study, high fat diet (HFD)-induced obese C57BL/6J mouse model was established for evaluation. The first set of study aimed to evaluate the role of mitochondrial dysfunction using Drp1 inhibitor Mdivi-1 and IL-4 as druggable agents. IL-4 and Mdivi-1 decreased body weight, liver weight, and fat weight in HFD mice. Increases of ALT, AST, fasting glucose, total cholesterol, triglycerides, and hepatic triglycerides were revealed in HFD mice and the increments were decreased by IL-4 and Mdivi-1. IL-4 and Mdivi-1 also displayed beneficial effects on liver histopathological abnormality glucose intolerance, insulin intolerance, IL-6 mRNA expression, MDA production, and circulating levels of Citrullinated Histone H3 and dsDNA. In the second set of study, roles of neutrophil extracellular traps PAD4 inhibitor Cl-amidine, STING inhibitor C-176, Sirt1 activator Resveratrol, and HMGB1 inhibitor Glycyrrhizic acid were further evaluated. Data revealed that Cl-amidine, C-176, Resveratrol, and Glycyrrhizic acid treatment had benefits in glucose intolerance, insulin insensitivity, and elevated total cholesterol. To evaluate changes of signaling molecules, proteins of liver, gastrocnemius, and epididymal fat tissues were examined by Western blot. The tested targets included P-AMPK, HMGB1, P-IRS1, P-TBK1, TLR4, PAD4, P-STING, STING, P-IRF3, cGAS, PI3K p85, Neutrophil elastase, P-IR , Glut4, RAGE, Sirt1, and P-Akt. In conclusion, using high fat diet-induced obesity mouse model, we found that mitochondrial dysfunction augmented disease progression of NAFLD. Peripheral Drp1 mitochondrial fission inhibitor Mdivi-1, PAD4 inhibitor Cl-amidine, STING inhibitor C-176, Sirt1 activator Resveratrol, HMGB1 inhibitor Glycyrrhizic acid, and IL-4 administration produce benefit and improves NAFLD. However, the underlying molecular mechanisms in details should be investigated furthermore.

Keywords：Diabetes mellitus; Mitochondrial dysfunction; Neutrophil extracellular traps; Obesity

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建立主動脈瓣與胸主動脈的自動圈註量測深度學習模型

Deep Learning for Automatic Segmentation of Aortic Valves and Thoracic Aorta

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臨床從醫學影像中獲得有用的定量指標的過程通常需要經驗豐富的醫生瀏覽許多影像，並手動標註感興趣的區域以便於定量化，這一過程既耗時又費力。 本計畫旨在利用人工智慧創建一個自動化標註模型，幫助臨床醫生減輕手動定量標註的負擔。模型的目標是精確分割主動脈瓣和整個胸主動脈。

本研究從 1769 筆案例中，以五個條件作為篩選標準：胸腹部 CT 掃描、有打顯影劑、影像數據完整、胸主動脈正常案例、胸主動脈瘤案例，篩選出 663 筆案例，其中正常案例有 301 筆，胸主動脈瘤案例有 362 筆。我們以開源 AI 模型 TotalSegmentator 作為基礎模型自動分割胸主動脈在打藥 CT 影像中的區域，接著自動偵測胸主動脈的起點與終點，計算出血管中心線，將整條血管拉直，最後計算胸主動脈拉直後的最長徑和截面積，並從整個數值序列中量化出兩者的最大值、最小值、平均值、中位數、四分位距，作為分類正常與異常案例的量化參數。

結果顯示除了最小值外，其他參數在正常與異常組的數值方面都有統計顯著意義，ROC 分析的曲線下面積為最長徑最大值、最小值、平均值、中位數、四分位距分別為 0.84, 0.51, 0.84, 0.82, 0.79，面積參數的則分別為 0.84, 0.50, 0.85, 0.82, 0.84。除了最小值參數外，其餘 ROC 下面積平均大於八成。

本研究顯示人工智慧自動量化胸主動脈的方法，對於分辨正常與胸主動脈瘤案例的任務，能夠達到不錯的效能，利用人工智慧自動胸主動脈量化方法，能夠輔助醫師做初步篩選出可能有疾病的案例，可做為臨床流程案例排序依據，減輕醫師瀏覽影像負擔。

關鍵詞：人工智慧；自動量化；胸主動脈；電腦斷層攝影血管攝影；TotalSegmentator

The process of obtaining useful quantitative indicators from medical images in clinical practice often requires experienced doctors to review many images and manually annotate areas of interest for quantification. This process is both time-consuming and labor-intensive. This project aims to use artificial intelligence to create an automated annotation model to help alleviate the burden of manual quantitative labeling for clinical doctors. The model's goal is precise segmentation of the aortic valve and the entire thoracic aorta.

This study selected 663 cases from 1769 cases using five criteria as screening standards: thoracoabdominal CT scans, use of contrast agents, complete image data, normal thoracic aorta cases, and thoracic aortic aneurysm cases. Among them, there were 301 normal cases and 362 thoracic aortic aneurysm cases. We used the open-source AI model TotalSegmentator as the base model to automatically segment the thoracic aorta region in contrast-enhanced CT

images. Subsequently, we automatically detected the starting and ending points of the thoracic aorta, calculated the blood vessel centerline, straightened the entire vessel, and finally calculated the longest diameter and cross-sectional area of the straightened thoracic aorta. From the entire series of values, we quantified the maximum, minimum, average, median, and interquartile range as quantitative parameters for classifying normal and abnormal cases.

The results showed that, except for the minimum value, other parameters had statistically significant differences in values between normal and abnormal groups. The area under the ROC curve for the maximum, minimum, average, median, and interquartile range of the longest diameter were 0.84, 0.51, 0.84, 0.82, and 0.79, respectively, while those for the area parameters were 0.84, 0.50, 0.85, 0.82, and 0.84, respectively. Except for the minimum value parameters, the rest averaged more than 80% in area.

This study demonstrates that the method of using artificial intelligence to automatically quantify the thoracic aorta can achieve good performance in the task of distinguishing between normal cases and thoracic aortic aneurysm cases. The use of artificial intelligence for automatic quantification of the thoracic aorta can assist doctors in preliminarily screening for potential disease cases, serving as a basis for case sorting in clinical workflows and reducing the burden of image review for doctors.

Keywords: Artificial Intelligence; Automated Quantification; Thoracic Aorta; Computed Tomography Angiography; TotalSegmentator

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使用深度學習在電腦斷層上勾畫海馬迴位置－立體空間影像配準與核磁共振資訊遷移

Hippocampus segmentation on CT using deep learning – 3D image registration and information transfer from MRI

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核磁共振(Magnetic resonance imaging ,MRI)利用強磁場和無線電波來創建大腦影像，以非侵入性的方式檢查人體內部器官，如腦部、肝臟等部位，提供了軟組織詳細且高解析度的影像。MRI 是檢查和診斷大腦結構的主要影像工具。然而，MRI 的組成複雜，對於新手醫師來說容易感到困惑，需要廣泛的學和經驗才能精準解讀 MRI 成像。

在 MRI 序列中，MP-RAGE(Magnetization Prepared Rapid Gradient-Echo ,MP-RAGE)提供精準的腦部結構資訊。因此我們收集了 50 組腦部 MP-RAGE 影像，包含 31 筆癲癇組及 19 筆對照組，並將 32 組影像分為訓練集，8 組為驗證集，10 組為測試集，訓練 Unet 模型。

在這項研究中，我們開發了一款快速自動圈註腦部結構的深度學習模型，命名為 Brian39，它能在一到兩分鐘內預測 39 個不同的腦部區域，Dice 值範圍從 0.94 到 0.99，從 Dice 值顯示，Brain39 能快速且精準的預測腦部區域，在臨床上能輔助醫師解讀 MRI 影像，提升精確判讀和診斷。

關鍵詞：癲癇；深度學習；預測和分割；腦部核磁共振；醫學影像

Magnetic resonance imaging (MRI) is a non-invasive medical imaging technique that provides detailed and high-resolution images of soft tissue. MRI is the primary imaging tool for examining and diagnosing structural abnormalities in the brain. However, deciphering MRI images needs extended learning and experience.

In the MRI sequences, different sequences provide distinct features of brain regions. The Magnetization Prepared Rapid Gradient- Echo (MP-RAGE) sequence provides precise information regarding brain structure.

To provide clinical practitioners a convenient tool for automated delineation of brain structures, we developed a deep learning model. In this study, we gathered 50 sets of brain MP-RAGE images, encompassing 31 epilepsy patients and 19 control subjects, of which 32 sets of images were in the training set, 8 sets were in the validation set.

We named the model Brain 39, and it can predict 39 different brain regions in one to two minutes. The Dice value ranging from 0.94 to 0.99, improving the efficiency of brain region segmentation in image processing.

Keywords: Brain MRI, Unet, Deep learning, Epilepsy, Medical imaging

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