馬 偕 紀 念 醫 院
專 題 研 究 計 畫 申 請 書

條碼編號 108DMH0100146

類別	院內計畫編號	計畫名稱	主持人
鼓勵型計畫		大腸腺瘤性瘜肉合併頸動脈內皮斑塊形成之新穎評估因子探究	胡光濬

核　　示		
院長	副院長（醫務）	醫學研究部主任
核示結果：☐ 通過　☐不通過 金額：　拾　萬　仟　佰　拾　元整		

◎計畫內容如涉及人體試驗或動物實驗或基因重組實驗,須自行向本院人體試驗委員會或實驗動物照護及使用小組或生物安全小組申請，審查通過後方可執行。

馬偕紀念醫院研究計畫申請書

一、基本資料：

計畫類別(單選)	鼓勵型計畫					
研究型別	個別型計畫					
計畫歸屬	醫學研究部					
申請機構/系所(單位)	馬偕紀念醫院台北院區特殊醫療單位健檢中心					
本計畫主持人姓名	胡光濬	職稱	主治醫師	身分證號碼	*******480	
本計畫名稱 中文	大腸腺瘤性瘜肉合併頸動脈內皮斑塊形成之新穎評估因子探究					
本計畫名稱 英文						
整合型總計畫名稱						
整合型總計畫主持人				身分證號碼		
全程執行期限	自民國 108 年 08 月 01 日起至民國 109 年 07 月 31 日					
研究學門(請參考本申請書所附之學門專長分類表填寫)	學門代碼	名稱(如為其他類，請自行填寫學門)				
	01	內科部				
研究性質	N/A					
本計畫是否有進行下列實驗：(勾選下列任一項，須附相關實驗之同意文件)						
計畫連絡人	姓名：胡光濬 電話：(公) 2861 (宅/手機) 0975835778					
通訊地址	台北市中正區廈門街 81 巷 34 號 2 樓					
傳真號碼	25418720	E-MAIL：	mimiandbear2001@yahoo.com.tw			

計畫主持人(申請人)簽章：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿　日期：＿＿＿＿＿＿＿＿＿＿＿＿＿＿

五、耗材、物品及雜項費用：

第 1 年　　金額單位：新台幣元

項 目 名 稱	說明	單位	數量	單價	金額	備註	經費執行單位
合　　計					0		

馬偕紀念醫院人體研究倫理審查委員會通知

胡光濬主持人您好：

關於您執行「大腸腺瘤性瘜肉合併頸動脈內皮斑塊形成之新穎評估因子探究」臨床試驗案 (本會編號: **18MMHIS185)**，經本會審查後於 2019 年 04 月 09 日通過，附件為本院人體研究倫理審查委員會同意函乙份，請查收。

以下是研究計畫通過審查後，於本院執行應注意之事項說明：

1. **為確保參與藥品臨床試驗之受試者權益，非因特殊性別所研發使用之藥物人體試驗計畫，其計畫受試者之單一性別比例不得低於三分之一，請確實依此原則辦理。(100.01.12 衛署醫字第 1000203890 號函)。**
2. 請於計畫執行前再次詳閱並遵行『藥品優良臨床試驗準則』。
3. 對於受試者的權益：每一位受試者在進入試驗前都應該獲得詳細的解釋並自願簽署受試者同意書，且每位受試者需持有一份副本，請您及您的研究團隊注意保護他們的隱私。
4. 本會所核發之臨床試驗證明書之效期，會於初審審查時決定，該研究須接受追蹤審查的頻率至少一年一次。
5. 依照 ICH-GCP 規定，臨床試驗計畫執行，每屆滿一年，人體研究倫理審查委員會必須重新審查是否繼續進行。請於同意臨床試驗證明書上所載明之有效期限到期一個月前繳交期中報告，以利本會進行審查。
6. 若您期中報告審查通過後，本會將會再發一張同意臨床試驗證明書。
7. 請依核准版本執行，並於計畫執行時以加蓋核准章之受試者同意書版本讓受試者簽署。
8. 若您有需要變更您的試驗計畫之任何內容(如:修改試驗計畫、變更受試者同意書、新增試驗協同主持人、招募廣告)，均需向本會提出變更申請。在您申請變更獲得核准前，您必須依照原先通過之計畫內容執行或暫停執行。
9. 關於試驗執行中發生之嚴重不良反應（SAE）其規定與通報時程：(依照「**藥品優良臨床試驗準則**」**第 106 條**規定辦理)

發生地點	通報時程	應檢附之文件
總院與各分院	1. 死亡或危及生命之嚴重不良事件：獲知日起 7 日內通報。	1. 本院 SAE 通報表 2. 衛生福利部 SAE 通報表格 3. 病歷摘要

	2. 其他非死亡或危及生命之嚴重不良事件：獲知日起 15 日通報	
國內其他醫院	獲知日起 15 日內提供詳細書面資料	1. 本院 SAE 通報表 2. 衛生福利部 SAE 通報表格 3. 病歷摘要
國外之試驗機構	獲知日起 30 日內通報	1. 通報之 SAE 個案清單 2. 多國多中心計畫之 SAE 通報表。 3. CIOMS Form(或其他相當之表格)

10. 在試驗計畫執行期間，若因故需提前中止/終止，請向本會提出中止/終止之申請，並繳交試驗報告。
11. 在試驗計畫執行結束時，須請您提交結案報告，**且應完整保存每個研究計畫相關審案資料且依規定保存至試驗結束後三年**。
12. **試驗執行期間，您所收納之受試個案其因試驗而產生之費用須由試驗委託者負擔，本院人體研究倫理審查委員會將給您此計畫專用之學術減免單，於收到學術減免單後始可使用，本會將依此進費用行核銷作業。**
13. **對於臨床試驗所需之藥品，僅可由本院藥局、試驗主持人及研究人員保管與發放，唯試驗藥品應妥善保管，發放藥品予受試者應重複核對，以善盡保護受試者之責。**
14. 臨床試驗相關之申請表格，請參考本院人體研究倫理審查委員會之網頁，網址為『http://www.mmh.org.tw/taitam/irb/index.htm』

若有試驗相關問題，請與本會聯絡(02-2543-3535 分機 3486~3488)，謝謝。

馬偕紀念醫院人體研究倫理審查委員會

2019.04.09

馬偕紀念醫院 M.M.H. APR 09 2019 人體研究倫理審查委員會 台北市中山北路二段92號

馬偕紀念醫院
人體研究倫理審查委員會同意臨床試驗證明書

No.92, Sec.2, Zhongshan N. Rd., Taipei City 10449, Taiwan
TEL:+886-2-2543-3535
FAX:+886-2-25219529

台北市中山北路二段92號
TEL:+886-2-2543-3535
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查以「大腸腺瘤性瘜肉合併頸動脈內皮斑塊形成之新穎評估因子探究」試驗案(本會編號:18MMHIS185)，已經本院人體研究倫理審查委員會審查通過，同意馬偕紀念醫院胡光濬醫師依所提計畫內容進行臨床試驗，本會組織與執行皆遵守ICH-GCP規範，特此證明。此計畫執行期限自2019年08月01日至2027年07月31日，同意函有效期限至2020年07月31日。(依照ICH-GCP規定，臨床試驗每屆滿一年，人體研究倫理審查委員會必須重新審查是否繼續進行。請於有效期限到期一個月前繳交期中報告以利本會進行審查)。

同意計畫之內容版本日期：

1. 詳細計畫書：Date 09-Apr-2019
2. 受試者同意書： Date 09- Apr -2019
3. 試驗執行地點：台北馬偕紀念醫院
4. 協同主持人：馬偕紀念胃腸內科主治醫師施壽全
5. 受試者人數:200

台灣基督長老教會馬偕醫療財團法人
馬偕紀念醫院人體研究倫理審查委員會(1)
主任委員　呂宜興

2019 年 04 月 09 日

MacKay Memorial Hospital

Institutional Review Board Approval of Clinical Trial

Apr.09, 2019

To Whom It May Concern ：

Protocol Title：Evaluation of novel risk factors of colon adenoma combined carotid artery plaque

IRB Number：18MMHIS185

Protocol Version Date：Date 09-Apr-2019

Informed Consent Form：Date 09- Apr -2019

Principal Investigator： Kuang-Chun Hu (MacKay Memorial Hospital)

Co-Investigator：Shou-Chuan Shih (MacKay Memorial Hospital)

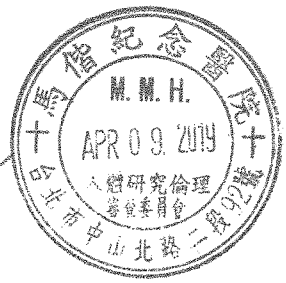
Trial Site: Taipei MacKay Memorial Hospital

Subjects:200

Above study has been approved by the MacKay Memorial Hospital Institutional Review Board on Aug.01, 2019 and valid till Jul.31, 2020. (period of Carry Out Approved Activities：Aug.01, 2019~ Jul.31, 2027) The constitution and operation of this review board are according to the guidelines of ICH-GCP. According to ICH-GCP, IRB will have to review each clinical research case annually and decide whether continue it or not. Therefore, please send us your Annual Report one month before the expiry date.

Yours Sincerely,

Yi-Shing Leu



Yi-Shing Leu, M.D.
Chairman,
Institutional Review Board (1),
MACKAY MEMORIAL
HOSPITAL, Taiwan.

請依核准版本執行

人體研究對象（或受試者）同意書

計畫名稱 中文：大腸腺瘤性瘜肉合併頸動脈內皮斑塊形成之新穎評估因子探究 英文：Evaluation of novel risk factors of colon adenoma combined carotid artery plaque	
研究機構：台北、淡水馬偕紀念醫院	委託單位/藥廠：無 研究經費來源：科技部
研究主持人：胡光濬醫師 職稱：胃腸肝膽內科/健檢中心主任/主治醫師 協同主持人：施壽全醫師 職稱：胃腸肝膽內科/教授/主治醫師	胡光濬 2019-01-28
24 小時緊急聯絡人：胡光濬醫師 電話：0975835778	
受試者姓名： 受試者編號： BH: cm. BW: kg 病歷號碼：	

您被邀請參與此研究，這份表格提供您本研究之相關資訊，研究主持人或其授權人員將會為您說明研究內容並回答您的任何疑問，在您的問題尚未獲得滿意的答覆之前，請不要簽署此同意書。您不須立即決定是否參加本研究，請您經過慎重考慮後方予簽名。您須簽署同意書後才能參與本研究。如果您願意參與本研究，此文件將視為您的同意紀錄。即使在您同意後，您仍然可以隨時退出本研究而不需任何理由。

(一) 研究目的：

本研究主要目的是評估，內毒素（endotoxin）、氧化三甲胺(TMAO)、血清素（serotonin）、短鏈脂肪酸（SCFAs）、大腸直腸癌相關基因多型性與蛋白質標記作為大腸腺瘤性瘜肉發生合併頸動脈斑塊形成新穎評估因子的可能性。

(二) 研究現況簡介：

高血糖合併幽門螺旋桿菌的感染時，對於大腸腺瘤性瘜肉的形成有加乘作用。高血糖合併幽門螺旋桿菌感染是同時發生頸動脈斑塊及大腸腺瘤的核心危險因子。幽門螺旋桿菌的存在與大腸腺瘤的形成有因果關係。根除幽門螺旋桿菌不僅僅是降低了消化性潰瘍及胃部惡性疾病的形成，也減少了大腸腺瘤性瘜肉發生。目前相關的臨床分子醫學評估因子少。

(三) 研究之納入與排除條件：

納入條件：

1. 說明後有意願參加之受試者（年齡 20-75 歲），新收案 200 人。
2. 收錄 2006 年 01 月 01 日～2018 年 09 月 30 日於馬偕健康檢查中心同時接受生理檢驗、無痛大腸鏡、頸動脈超音波分析的健康受檢者（年齡 20-75 歲）。
3. 病例回溯符合條件之個案
4. 16MMHIS066 之去連結檢體
5. 台灣人體生物資料庫所釋出之資訊

排除條件：

1. 曾經罹患大腸癌及大腸癌家族史；2. 曾有大腸瘜肉及家族性瘜肉病史；3. 潰瘍性結腸炎及克隆氏疾病患者；4. 正接受 Aspirin 或長期服用 NSAID 者；5. 有頸動脈內皮斑塊病史；6. 經說明後不願意參加者；7. 孕婦；8. 愛滋病者

(四) 本研究方法及相關程序：

MMH IRB 2019-04-09 核准章

1. 由受試者的接受健康檢查時多留一管血，並收集糞便檢體中的剩餘檢體。
2. 血液萃取 DNA 進行基因多型性檢測比對。
3. 分離後的血漿及糞便進行內毒素（endotoxin）、三甲基胺氧化物(TMAO)、血清素（serotonin）、短鏈脂肪酸群（SCFAs）、大腸直腸癌相關蛋白質標記鑑定。
4. 基因遺傳統計對照資料：來自 A.“台灣地區華人細胞株及基因資料庫建立調查研究計畫”所收集及建立之超級對照組(Super Control) (Pan WH, Fann CS, Wu JY, Chen YT, et al. (2006) Har. Chinese cell and genome bank in Taiwan: purpose, design and ethical considerations. Human Hered 61:27-30) 去連結資料。B. 台灣人體生物資料庫 (Taiwan Biobank) 所搜集之台灣人體生物資訊。據此統合分析全基因頻度與其他因子在膽石症患者的異同，預測可能的致病機轉，改善疾病的診斷和治療。

(五) 可能產生之副作用及其發生率與處理方法：

1. 與研究過程相關的副作用(風險)及發生率

   可能的併發症或危險有心理害怕 (10%)、抽血傷口疼痛 (90%)、出血 (10%)、瘀青 (5%)、腫脹 (5%) 或感染 (0.001%)。

2. 與研究過程相關的副作用(風險)處理方法

   我們會細心，用最純熟的無菌技術，以減少疼痛，並避免感染。抽血後，請按壓抽血處5分鐘以上，使傷口不致流血。也請勿污染傷口，以免感染。萬一出血不止或感染，我們會立即給與治療。

(六) 其他替代療法及說明：

不適用

(七) 研究預期效益：

若能經由此研究而檢出容易罹患這些疾病或併發症的個體，會對大家有下列好處：(1) 增進對該疾病的預測能力，(2) 做為擬定疾病篩檢之依據，(3) 更了解疾病致病的機轉。這不但有益於自己和自己的家族，而且有助於全體國人，更能促進醫學的進步。

(八) 研究進行中受試者之禁忌、限制與應配合之事項：

抽血，8 毫升 (ml, cc)和因醫療需要而檢驗的剩餘血液檢體。禁忌為有嚴重出血傾向者。

(九) 受試者個人資料之保密：

馬偕紀念醫院將依法把任何可辨識您的身分之記錄與您的個人隱私資料視為機密來處理，不會公開。研究人員將以一個研究代碼代表您的身分，此代碼不會顯示您的姓名、國民身分證統一編號、住址等可識別資料。如果發表研究結果，您的身分仍將保密。您亦瞭解若簽署同意書即同意您的研究資料可直接受監測者、稽核者、本院人體研究倫理審查委員會及主管機關檢閱，以確保研究過程與數據符合相關法律及法規要求，上述人員並承諾絕不違反您的身分之機密性。除了上述機構依法有權檢視外，我們會小心維護您的隱私。

(十) 研究之退出與中止：

您可自由決定是否參加本研究；研究過程中也可隨時撤回同意，退出研究，不需任何理由，且不會引起任何不愉快或影響其日後醫師對您的醫療照顧。研究主持人或贊助廠商亦可能於必要時中止或終止該研究之進行。

MMH IRB
2019 -04- 09
核准章

(十一) 損害補償與保險：

研究一定有風險，為確保因為參與研究發生不良反應致造成您的損害時所可能獲得之

保障，請您務必詳閱本項說明內容：

1. 如依本研究所訂臨床研究計畫，因發生不良反應造成損害，由（馬偕紀念醫院）負補償責任。但本受試者同意書上所記載之可預期不良反應，不予補償。
2. 如依本研究所訂臨床研究計畫，因而發生不良反應或損害，本醫院願意提供專業醫療照顧及醫療諮詢。您不必負擔治療不良反應或損害之必要醫療費用。
3. 除前二項補償及醫療照顧外，本研究不提供其他形式之補償。若您不願意接受這樣的風險，請勿參加研究。
4. 您不會因為簽署本同意書，而喪失在法律上的任何權利。
5. 若您已經擁有其他種醫療相關、健康相關商業保險或失能險，加入此臨床研究可能會影響已擁有之商業保險的權益，本研究無法承諾或保證您此部分的權益受影響的程度。
6. 本研究沒有投保人體研究保險。

若您確因參與本研究因而發生不良反應造成之損害，前述補償包括合理的醫療費用，惟應符合以下條件：您依研究主持人之指示參與過程；您的損害並非故意造成；您遵守研究主持人之建議。

(十二) 受試者之檢體(含其衍生物)、個人資料之保存、使用與再利用

1. 個人資料之保存與使用

對於您檢體之基本資料及試驗結果，計畫主持人 胡光濬 主治醫師會遵守保密義務。您的檢體會以編碼標示（編碼：以數字或英文字母等代碼，取代檢體提供者姓名、國民身份證統一編號、病歷號等可供辨識個人資訊之作業方式），任何測試者皆無法辨認檢體來源，並且在未經您同意的情況下，計畫主持人不會洩漏任何可能辨認您的訊息。除主持人、協同主持人、共同研究人員得查看受試者及試驗相關資料外，稽核者、人體研究倫理審查委員會和政府查核者得檢視，以確保臨床試驗過程與數據符合相關法律及法規之要求。其他人無法接觸到受試者資料。和本研究有關之報告，或其他任何科學文獻研討會上發表的論文，決不會公布受試者之姓名身份及基本資料。編碼與檢體所屬者之連結資料，則由剩餘檢體庫管理人另行記錄。然而，去連結即完全永久消除，並已無從辨識檢體所屬之個人。

2. 檢體(含其衍生物)之保存與使用

檢體保管於馬偕紀念醫院淡水院區醫學研究部分子醫學研究組，保管者為施壽全，聯絡電話 0975835778，email: scchuan@mmh.org.tw；檢體使用者：胡光濬、施壽全

檢體保存期限：自收案日起八年，時效截止時依下列「去連結」處理或在第三方見證者監督下進行銷毀。

3. 剩餘檢體之保存與再利用

原特定目的之試驗結束後或您要中途退出，剩餘檢體將由馬偕紀念醫院或試驗主持人銷毀。但您也可選擇另一種處理方式：

☐ 同意不銷毀，交由馬偕紀念醫院做「去連結」處理，任何可供辨識個人資訊與對照資料會完全永久消除。已無從辨識檢體所屬之個人，因此未來進行特定研究計畫時，將不再尋求您的同意，檢體去連結後，您也無法再撤銷此一同意。

檢體提供者/法定代理人簽署:_____日期:_____

(十三) 受試者權利：

1. 如果您在研究過程中對研究工作性質產生疑問，對身為患者之權利有意見或懷疑因參與研究而受害時，可與本院人體研究倫理審查委員會聯絡請求諮詢，電話號碼為：(02)2543-3535轉3486～3488。

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2. 研究過程中，與您的健康或是疾病有關，可能影響您繼續接受臨床研究意願的任何重大發現，都將即時提供給您。如果您決定退出，研究主持人會安排您繼續接受醫療照護。如果您決定繼續參加研究，可能需要簽署一份更新版的同意書。
3. 為進行研究工作，您必須接受_____醫師的照顧。如果您現在或於研究期間有任何問題或狀況，請不必客氣，可與在馬偕醫院胃腸肝膽內科的胡光濬醫師連絡（24小時聯繫電話：0975835778）。
4. 本同意書一式2份，研究主持人或其授權人員已將1份已簽名的同意書副本交給您，並已完整說明本研究之性質與目的。研究主持人或其授權人員已回答您有關本研究的問題。
5. 參加本研究計畫之補助：無
6. 基因檢測過程中，如有非預期之結果產生, 但可能對治療或將來疾病預防照顧有影響。我們會在結果出現後，您下次門診時向您告知。
7. 若試驗結束後 8 年內，發現有非預期且直接影響您的安全疑慮，亦將通知您。

(十四) 本研究預期可能衍生之商業利益：

如本研究計畫成果作學術文獻發表或取得智慧財產，您同意馬偕紀念醫院得無條件以之作為從事疾病診斷、預防、治療及研究等醫學用途。

(十五) 簽名：

1. 研究主持人、或協同主持人或其授權人員已詳細解釋有關本研究計畫中上述研究方法的性質與目的，及可能產生的危險與利益。

研究主持人/協同主持人簽名：_____ 日期：_____年____月____日

在取得同意過程中其他參與解說及討論之研究人員簽名：_____日期：__年__月__日

2. 經由說明後本人已詳細瞭解上述研究方法及可能產生的危險與利益，有關本研究計畫的疑問，亦獲得詳細解釋。本人同意接受並自願參與本研究，且將持有同意書副本。

受試者簽名：_____ 日期：____年__ 月__ 日 出生年月日： _____年__月__日

電話： 國民身分證統一編號： 性別：

通訊地址：

見證人簽名：_____ 日期：_____年___月___日 與受試者關係：

電話： 通訊地址：

- 受試者、法定代理人或有同意權之人皆無法閱讀時，應由見證人在場參與所有有關受試者同意之討論。並確定受試者、法定代理人或有同意權之人之同意完全出於其自由意願後，應於受試者同意書簽名並載明日期。試驗相關人員不得為見證人。

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個人資料表

以下各項資料均將收錄於本系統資料庫內，其中有關個人的姓名、服務機關、連絡電話(公)及論文著述等，將公開於網際網路「研究人員」項下，提供外界查詢。至於其他如傳真、E-mail、學歷、經歷、專長等資料，為尊重個人意願，請圈選（同意、不同意）於網際網路上提供外界查詢。（如以往已經表示過意見者，可不必再勾選）。

一、 基本資料

身份證號碼	*******480				
中文姓名	胡光濬	英文姓名	Kuang Chun Hu		
國籍	中華民國	性別	M	出生日期	197*年 0*月 1*日
聯絡地址	100 台北市中正區廈門街 81 巷 34 號 2 樓				
聯絡電話	(公).0975835778		(宅/手機).2861		
傳真號碼	25418720	E-MAIL	mimiandbear2001@yahoo.com.tw		

二、 主要學歷 由最高學歷依次填寫，若仍在學者，請在學位欄填「肄業」。

學校名稱	國別	主修學門系所	學位	起訖年月(西元年/月)
國立台灣大學	中華民國	臨床醫學研究所	博士	2013/07 至 2018/06
國立台灣大學	中華民國	臨床醫學研究所	碩士	2011/07 至 2013/06
高雄醫學大學	中華民國	學士後醫學系	學士	1996/09 至 2001/06

三、 現職及與專長相關之經歷 指與研究相關之專任職務，請依任職之時間先後順序由最近者往前追溯。

服務機構	服務部門／系所	職稱	起訖年月(西元年/月)
現職：馬偕紀念醫院台北院區	健檢中心	主治醫師	2006/07
經歷：馬偕紀念醫院	台北健檢中心	主任	2015/01 至 0/

四、 專長 請自行填寫與研究方向有關之學門及次領域名稱。

1. 消化學	2.	3.	4.

科技部專題研究計畫申請書

申請條碼：108WHK0910031

一、基本資料：

計畫類別（單選）	一般研究計畫				
研究型別	個別型				
計畫歸屬	生科司				
申請機構/系所（單位）	台灣基督長老教會馬偕醫療財團法人馬偕紀念醫院內科				
本計畫主持人姓名	胡光濬	職稱	主治醫師(滿二年)	身分證號碼	A12159****
本計畫名稱 中文	大腸腺瘤性瘜肉合併頸動脈內皮斑塊形成之新穎評估因子探究				
本計畫名稱 英文	Evaluation of novel risk factors of colon adenoma combined carotid artery plaque				
整合型總計畫名稱					
整合型總計畫主持人				身分證號碼	
全程執行期限	自民國 108 年 08 月 01 日起至民國 110 年 07 月 31 日				
研究學門	學門代碼	學門名稱			
	B10H001	肝膽胃腸			
研究性質	□純基礎研究 □導向性基礎研究 ■應用研究 □技術發展				
【請考量己身負荷，申請適量計畫】 本年度申請主持科技部各類研究計畫(含預核案)共 1 件。(共同主持之計畫不予計入)					
本計畫是否為國際合作研究：■否； □是，請加填表IM01~IM03					
本計畫是否申請海洋研究船：■否； □是，請務必填寫表CM15。					
1.本計畫是否有進行下列實驗/研究：（勾選下列任一項，須附相關實驗/研究同意文件） ■人體試驗/人體檢體 □人類胚胎/人類胚胎幹細胞 □基因重組實驗 □基因轉殖田間試驗 □第二級以上感染性生物材料 □動物實驗(須同時加附動物實驗倫理3R說明) 2.本計畫是否為人文司行為科學研究計畫：□是(請檢附已送研究倫理審查之證明文件)； □否 3.本計畫是否為臨床試驗研究計畫：■是(請增填性別分析檢核表CM16)； □否					
計畫連絡人	姓名：胡光濬 電話：(公) 02-25433535 (宅/手機) 0975835778				
通訊地址	台北市中正區螢圃里16鄰廈門街81巷34號2樓				
傳真號碼	02-25232448	E-MAIL	mimiandbear2001@yahoo.com.tw		

計畫主持人簽章：＿＿＿＿＿＿＿＿　　日期：＿＿＿＿＿＿＿＿

二、研究計畫中英文摘要：請就本計畫要點作一概述，並依本計畫性質自訂關鍵詞。

計畫中文關鍵詞	大腸腺瘤性瘜肉、頸動脈斑塊、人類白血球抗原組織複合體、短鏈脂肪酸、大腸癌蛋白質標記、大腸癌基因多型性、總體基因體學
計畫英文關鍵詞	colon adenoma, carotid artery plaque, Human Leukocyte Antigen (HLA), short-chain fatty acids (SCFAs), Metagenomics, single nucleotide polymorphism (SNP), colon cancer protein biomarkers
計畫中文摘要	我們先前的發表指出：性別、年紀、身體質量指數(BMI)、幽門螺旋桿菌(H. pylori)感染及醣化血色素(HbA1c)是形成大腸腺瘤的危險因子。不論有無幽門螺旋桿菌感染，大腸腺瘤的發生率都會隨著HbA1c的上升而增加(HbA1c ≥ 6.5 %, 57.1% vs 32.5%)。而有感染的受檢者，上升的比例更高。當受檢者年齡大於60 歲，男性，BMI 大於27，LDL > 130 mg/dL，HbA1c大於6.5%，高敏感性C反應蛋白大於0.3 mg/L，H. pylori感染陽性，以及使用高血壓控制藥物等，都是造成合併大腸腺瘤性瘜肉及頸動脈斑塊形成的危險因子。當 HbA1c大於6.5%；合併產生大腸腺瘤性瘜肉及頸動脈斑塊的勝算比上升到3.51; 95% CI, 1.97 – 6.25; p < 0.0001)。而對於幽門螺旋桿菌感染陽性者，相較於HbA1c正常者，當醣化血色素介於5.7% – 6.4%，合併產生大腸腺瘤性瘜肉及頸動脈斑塊的風險為 3.65; 95% CI, 2.32–5.73; p < 0.0001)，當醣化血色素大於6.5%，相對於未感染幽門螺旋桿菌且醣化血色素正常者，其合併產生大腸腺瘤性瘜肉及頸動脈斑塊的風險甚至上升到15 倍以上(OR：15.87, 95% CI, 8.66–29.08; p <0.0001)。因此，高血糖合併幽門螺旋桿菌的感染時，對於大腸腺瘤性瘜肉的形成有加乘作用，也是合併發生頸動脈斑塊及大腸腺瘤的核心危險因子。持續治療幽門螺旋桿菌感染能有效預防大腸息肉生成，轉化大腸癌；且可能降低頸動脈斑塊生成。但臨床上對於大腸腺瘤性瘜肉合併頸動脈內皮斑塊形成之評估因子除了已知的標記外，分子層次上的瞭解卻不多。本研究主要目的是評估，人類白血球抗原組織複合體鑑別、大腸癌基因多型性平台、大腸癌蛋白質標記、短鏈脂肪酸(SCFAs)、總體基因體學(metagenomics)作為大腸腺瘤性瘜肉發生合併頸動脈斑塊形成新穎評估因子的可能性。
計畫英文摘要	Our previous results revealed male sex, age, BMI, H. pylori infection, and an HbA1c level ≥ 6.5% as risk factors for adenomas. The prevalence of adenoma was increased in patients with elevated HbA1c levels in both H. pylori -positive and -negative groups (HbA1c≥ 6.5 %, 57.14% vs. 32.47%). The OR for adenoma was 1.44 (95% CI, 1.20–1.73) in H. pylori-positive patients or 1.68 (95% CI, 1.05–2.70) in H. pylori -negative patients with HbA1c≥ 7.0%. If both conditions were present, the OR was 4.79 (95% CI, 2.92–7.84). We found that age ≥ 60 years, male sex, BMI > 27, LDL > 130 mg/dL, HbA1c ≥ 6.5%, hs-CRP > 0.3 mg/L, and H. pylori infection were independent risk factors for synchronous colorectal adenoma and carotid artery plaque formation. The OR for synchronous colon adenoma and carotid artery plaque was significantly higher in the participants with HbA1c levels of 5.7%–6.4% and HbA1c ≥ 6.5% than in those with normal HbA1c in the H. pylori-negative group. The OR was increased further in H. pylori -positive patients when the HbA1c level ≥6.5% was 15.87 (95% CI, 8.661–29.082; p<0.0001). Hyperglycemia combined with H. pylori infection was an increased risk factor for synchronous colorectal adenoma and carotid artery plaque formation. H. pylori eradication not only decreased the incidence of gastric malignancy disease but also reduced the likelihood of colorectal adenoma development. Diabetes control may be warranted in higher prevalence areas. Persistently infected subjects had a higher colorectal adenoma risk than those with successfully eradicated infection. The benefit of H. pylori eradication was not only in reducing gastric malignancy disease but also in decreasing colorectal adenoma probability. However, evaluation factors of colon adenoma combined

	carotid artery plaque still limited in molecular level. In this study, we will compare multiple molecular factors as endotoxin, trimethylamine-N-oxide (TMAO), serotonin, short-chain fatty acids (SCFAs), metagenomics、colon cancer genetic polymorphism, and protein markers to evaluate colon adenoma combined carotid artery plaque.
計畫概述	請概述執行本計畫之目的及可能產生對社會、經濟、學術發展等面向的預期影響性(三百字以內)。 ※此部分內容於獲核定補助後將逕予公開
	大腸瘜肉與頸動脈斑塊是導致腦梗塞及大腸癌風險增加的潛在因子。表示會有更多的病患，先後受到這兩種疾病所苦。我們有責任將可能罹患這兩種疾病的受檢者利用分子標記、基因鑑別及早篩選出來，給予醫療上的介入，保障國人的健康。在社會上可以保護更多家庭的健康；在經濟上可以減少醫療資源浪費；在學術研究上更了解疾病發展的機轉，促進人類健康。

三、研究計畫內容（以中文或英文撰寫）：

Evaluation of novel risk factors of colon adenoma combined carotid artery plaque

大腸腺瘤性瘜肉合併頸動脈內皮斑塊形成之新穎評估因子探究

Colorectal cancer (CRC) is the third most common malignancy in men (10.0% of the total), the second in women (9.2% of the total), and the fourth leading cause of cancer-related death worldwide [1]. CRC is the top 1 cancer disease ranking in Taiwan 2016 (DOH, 2018/12/27. Figure 1). Colorectal adenomatous polyps are recognized as premalignant lesions that develop into CRC through the adenoma-to-carcinoma sequence [2]. Risk factors for colorectal adenoma include age, gender, obesity, dyslipidemia, impaired glucose tolerance, a family history of CRC, smoking, diet, daily activity, and *Helicobacter pylori* (*H. pylori*) infection [3-7]. Discrepancies have also been seen in the results of meta-analysis, with some demonstrating a positive association between *H. pylori* infection and colon adenoma [8, 9], whereas no statistical association between *H. pylori* infection and risk of colorectal neoplasm on East Asian [10]. These inconsistent results challenge the hypothesis of an association between *H. pylori* infection and colon adenoma. The pathogenic mechanisms responsible for a putative association remain unclear, although some have suggested possible confounding by a third factor [11]. Type 2 diabetes mellitus is also considered a risk factor for colon adenoma and carcinoma. Several case-control studies and meta-analysis reported that subjects with diabetes had an odds ratio (OR) of 1.45 for colon adenoma [12] and a relative risk of 1.38 for colorectal adenocarcinoma [13]. Unlike the possible association between *H. pylori* infection and colorectal neoplasm, the mechanism by which diabetes might increase colorectal neoplasm has been studied more extensively. One proposed mechanism is that hyperinsulinemia resulting from insulin resistance may directly promote carcinogenesis by stimulating colonic cell growth [14]. The hyperinsulinemia associated with diabetes is thought to lead to carcinogenesis through increased levels of insulin-like growth factor 1 (IGF-1), which increases cell proliferation and inhibits apoptosis, thus promoting tumor growth [15]. Diabetes is one of the most common metabolic disorders in the world, with a rapid increase in prevalence in the last decades [16]. If diabetes indeed increases the risk of colon adenoma, the prevalence of those neoplasms may also be expected to increase. Past studies of colorectal adenoma risk factors have looked at *H. pylori* infection or diabetes alone. Kim et al. [17] found that abdominal obesity among the individual components of metabolic syndrome was an important risk factor for colorectal adenoma. Tseng et al. [18] reported that the prevalence of colonic neoplasms was higher in patients with hyperglycemia (26.6 vs. 16.5%, $P < 0.001$). We also demonstrated that the prevalence of colorectal adenomas in patients who were *H. pylori*-positive and *H. pylori*-negative was 37.3% and 27.29%, respectively. Multivariate logistic regression analysis identified male sex, age, body mass index, *H. pylori*

infection, and HbA1c≥6.5% as independent risk factors for adenoma; use of hypoglycemic agents decreased this risk. The prevalence of adenoma was increased with elevated HbA1c levels regardless of *H. pylori* status. The OR for adenoma was 1.44 (95% confidence interval [CI], 1.20 to 1.73) if *H. pylori* was present or 1.68 (95% CI, 1.05 to 2.70) in patients who were *H. pylori*-negative but had HbA1c ≥7.0%. If both conditions were present, the OR was 4.79 (95% CI, 2.92 to 7.84). A 1%increase in HbA1c was associated with an increased prevalence of adenoma by 42.4% in *H. pylori*-positive subjects[19]. Thus, hyperglycemia status combined with *H. pylori* infection had a synergistic effect on the risk for colon adenoma [19]. The CRC incidence and mortality rates vary widely worldwide, and stabilizing or decreasing trends is seen in highly developed countries. In developing countries, however, the CRC incidence and mortality have also increased [20]. Therefore, identification of risk factors of colorectal adenomatous polyps will improve in prevention of CRC.

Over the past decades, patients who had coronary artery disease have been found to be at increased risk of developing colon adenoma [21, 22]. The lifetime risk of acute myocardial infarction is 30% and of stroke is 40% in Western countries [23, 24]. These two diseases are related to arthrosclerosis and are types of cardiovascular disease (CVD). Several studies have shown that carotid artery plaque formation increased the risk of CVD [25, 26]. CVD and CRC share similar risks factors, including gender, aging, hyperglycemia, smoking, hyperlipidemia, and obesity [27, 28]. In a recent study, the mortality rate of CVD had decreased slightly. These findings may have been related to more public bans on smoking and lower target levels of low-density lipoprotein cholesterol and blood pressure that contributed to improved control of risk factors over time [29]. In our previous study, total 2361 subjects were enrolled. Multivariate analysis including age ≥ 60 years, male sex, BMI > 27, LDL > 130 mg/dL, HbA1c ≥ 6.5%, hs-CRP > 0.3 mg/L and *H. pylori* infection were independent risk factors for synchronous colorectal adenoma and carotid artery plaque formation. In the *H. pylori*-positive and -negative groups, the proportions and OR for synchronous colon adenoma and carotid artery plaque increased with increasing HbA1c. OR for synchronous colon adenoma and carotid artery plaque was significantly higher in the participants with HbA1c levels of 5.7%–6.4% and HbA1c ≥ 6.5% than in those with normal HbA1c in the *H. pylori*-negative group. The OR was more significant increased for *H. pylori*-positive patients when HbA1c level ≥ 6.5% was 15.87 (95% CI 8.661–29.082, $p < 0.0001$)[30].

Helicobacter pylori infection is one of most common infectious diseases in humans, with an estimated overall prevalence in middle-aged adults of 74% in developing and 58% in developed countries [31]. *H. pylori* infection has been associated with colon adenoma formation [32] and with an increased incidence of ischemic stroke [33, 34]. The connection between *H. pylori* infection and gastric cancer had been proved [35]. Several large-scale studies have shown that *H. pylori* infection increased the risk of colorectal adenoma by 1.3- to 2.26-fold [32, 36, 37]. However, Machida-Montani et al. [38] and

Liou et al. [39] have both reported that *H. pylori* infection did not significantly increase the risk of colorectal adenoma. Most studies concerning the association between *H. pylori* infection and colorectal adenoma lacked cause and effect discussions because of cross-sectional study designs. Hyperglycemia has been associated with a higher prevalence of colon adenoma and CVD [18, 40]. This means that *H. pylori* infection and hyperglycemia may be common risk factors of CVD and CRC. Because the mortality for these two severe diseases has decreased, we can expect that patients who have survived one of these diseases may eventually develop the other. However, some patients may simultaneously develop colorectal adenoma and CVD. For physicians, the ability to "see the future" is valuable [41]. It is challenging to predict if a patient will develop CRC after developing CVD, especially in the early stage, such as colon adenoma and carotid artery plaque. Previous studies have shown a close relationship between CVD and CRC [21, 22] and that these two diseases shared similar risk factors such as gender, aging, smoking, hyperglycemia, and *H. pylori* infection [27, 28, 32-34]. In these factors, hyperglycemia and *H. pylori* infection have more possibility to be modified by medical intervention and can be treated with appropriate medicine. In our previous study, we found that *H. pylori* infection and hyperglycemia were involved in colon adenoma formation and had a synergistic effect [19]. This result hinted us that these two risk factors combined may affect other serious diseases such as CVD. There are few reports on more detailed interactions between the risk factors of these diseases. There have been no reports on the types of patients at higher risk for development of these two severe diseases either simultaneously or sequentially.

Our study is the first to address longitudinal time-related changes with respect to the progression of colon disease with and without *H. pylori* infection [32, 36-39]. We assessed the longitudinal effect of *H. pylori* infection and the progression of colorectal adenoma as measured using bidirectional endoscopy on the same day. During follow-up, the incidence rates of colorectal adenoma progression in participants with persistent *H. pylori* infection (persistent group) and those after successful eradication of this bacterium (eradication group) were 160.52 and 51.60 per 1000 person-years, respectively ($P = 0.0003$). After adjustment for confounding factors, the eradication group exhibited a higher risk of colorectal adenoma than the persistent group (hazard ratio = 3.34, 95% CI 1.899, 5.864). The colorectal adenoma ratio of patients uninfected with *H. pylori* was similar to that of the eradication group (23.93% vs. 20.12%, $P = 0.328$).[42]

Figure 1. Top 10 cancer ranking in Taiwan 2016. Colorectal cancer is top 1. (from DOH, 2018)

We already known the hyperglycemia, *H. pylori* infection are the risk factors in Taiwan[19, 30, 42, 43]. **However, limited prediction factors of colon adenoma combined carotid artery plaque in molecular level. Here, we will try to find novel risk factors to predict colon adenoma combined carotid artery plaque and prevention disease progression for the precision medicine in the near future. We design 2-year project to approaching our goal.**

Human Leukocyte Antigen (HLA) class II genotyping

One of the outstanding features of HLA genes is that they exhibit the highest degree of polymorphism among human functional genes. Hundreds to thousands of alleles have been identified at the loci encoding HLA class I and class II (*HLA-DR*, *-DQ*, and *-DP*) molecules, some of which exist in particular preferential combinations known as "common HLA haplotypes" in a relatively ethnicity-specific manner. Lower expression of HLA-DR+ T cell may increase carotid intraplaque neovascularization and atherosclerotic burden [44]. Colon adenoma, both *HLA-DR*, *-DQ* mono antigen can be detected in different types of colon adenoma [45]. But not comprehensive HLA

class II typing in colon adenoma, carotid artery plaque. These findings will be essential for future analysis to clarify the mechanisms of the immune recognition of carcinogenesis antigens by HLA class II molecules.

Discovery of genetic risk variants for colon adenoma and carotid artery plaque

Genome-wide association studies (GWASs) for sporadic CRC, which constitutes the majority of cases, have identified ~60 association signals at over 50 loci [46-50]. Yet most of the genetic factors contributing to CRC risk remain undefined. This severely hampers our understanding of biological processes underlying CRC. It also limits CRC precision prevention, including individualized preventive screening recommendations and development of cancer prevention drugs. The contribution of rare variation to sporadic CRC is particularly poorly understood.

To expand the catalog of CRC risk loci and improve our understanding of rare variants, genes and pathways influencing sporadic CRC risk and risk prediction, we will select Han Chinese specific SNPs according to the known database of CRC compared to Taiwan Biobank released data, perform with the Sequenom MassARRAY study. SNP selection criteria see in Method. This SNP panel will also test in carotid artery plaque.

Plasma Circulation Biomarker Test

Our preliminary data shown that endotoxin, serotoxin may not be a suitable index in colon adenoma and carotid artery plaque. The gut microbiota-derived metabolite, trimethylamine N-oxide (TMAO) plays an important role in cardiovascular disease (CVD). The fasting plasma TMAO was shown as a prognostic indicator of CVD incident in patients and raised the interest of intervention targeting gut microbiota. Wu WK et al. identify TMAO-producer phenotype of gut microbiota and may serve as a personal guidance in CVD prevention and treatment [51]. The MILLIPLEX(®) MAP Human Circulating Cancer Biomarker Magnetic Bead Panel comprises the tumor markers carcinoembryonic antigen, alpha-fetoprotein, total prostate-specific antigen, cancer antigen 15-3, cancer antigen 19-9, cancer antigen 125, cytokeratine 19-fragment, β-human chorionic gonadotropin, human epididymis protein 4, osteopontin, prolactin, the cell death and angiogenesis markers soluble Fas, soluble Fas-ligand, tumor necrosis factor related apoptosis-inducing ligand, vascular endothelial growth factor and the immunological markers interleukin-6 (IL-6), IL-8, tumor necrosis factor-α, transforming growth factor α, fibroblast growth factor-2, macrophage migration inhibitory factor, leptin, hepatocyte growth factor, and stem cell factor [52, 53]. We will determine intra- and inter-assay imprecision as well as dilution linearity using quality controls and serum pools. We will use this panel to test sample from colon adenoma and carotid artery plaque.

Plasma short-chain fatty acid (SCFAs) profiles in colon adenoma and carotid artery plaque

Short chain (C2-C6) fatty acids (SCFAs) are produced in the colon through bacterial fermentation of mainly dietary fiber. Butyrate (C4) possesses antineoplastic effects on human colon carcinoma cells, and epidemiological studies indicate that high fiber diets may reduce the incidence of colorectal cancer [54, 55]. The role of dietary fiber during colorectal carcinogenesis might therefore be related to its fermentation to butyrate. Faecal concentrations of total SCFAs and concentrations and ratios of the individual C2-C6 fatty acids did not differ between disease and control [56]. Therefore, Acetic acid, lactic acid, propionic acid (PA), butyric acid, isobutyric acid, valeric acid (VA), isovaleric acid (iso-VA), pivalic acid (tert-butyl-VA), and caproic acid (CA) will be tested in plasma, wash fluid before colonoscopy and find the correlation with carotid artery plaque.

Metagenomics analysis in colon adenoma

Several studies have examined the influence of differences in naturally occurring, complex gut microbiota (GM) on the initiation (colon adenoma) and development of CRC. Huge databases for 16S rRNA genes as well as for GM functions have been established as a resource for other studies in the field. We will capitalized on such data to run an analysis of stool fluid before colonoscopy from Han Chinese Taiwan in healthy examination check with colon adenoma that show subtle differences in the microbiota composition at the Operational Taxonomic Units (OTUs) level when compared to healthy individuals [57, 58].

研究方法、進行步驟及執行進度

Study Population

We conducted a retrospective cohort analysis of adults 40 years or older who underwent routine health examination at MacKay Memorial Hospital, Taipei, Taiwan, between July 2006 and December 2018. In Taiwan, the Industrial Safety and Health Law requires annual or biennial health screenings of all employees. Asymptomatic participants underwent esophagogastroduodenoscopy (EGD) and colonoscopy to detect gastrointestinal lesions. Asymptomatic individuals underwent bidirectional endoscopy (complete colonoscopy and EGD) on the same day. The EGD was performed first, and the colonoscopy was performed immediately after. The urease test for *H. pylori* was completed during the EGD procedure. Carotid artery ultrasound survey was also arranged on the same day or within 12 months of colonoscopy when the participants accepted annual physical checkups. Those who underwent at least two screening examinations were considered for analysis. The Institutional Review Board of the MacKay Memorial Hospital approved this study and waived the requirement for informed consent because we solely used anonymized data collected during routine screenings. Per the inclusion criteria, the study included participants over 40 years old who underwent a screening colonoscopy, EGD, a urease test to detect *H. pylori* infection, and carotid artery plaque screening.

Clinical Data Collection and Questionnaire

At each visit, clinical data, including fasting plasma glucose (Glucose AC), hemoglobin A1C (HbA1c), triglyceride, and low-density lipoprotein (LDL), were obtained from the participants on the same health checkup day as when the EGDs and colonoscopies were performed. Baseline characteristics (age, sex, height, weight, personal medical history, current medications, method of *H. pylori* eradication, family history of first degree relatives, smoking, highest educational attainment, occupation, income) were obtained from a questionnaire completed during the examination. We constructed composite indices for socioeconomic class on the basis of occupation, education (applying the Hollingshead index), and income. Five occupational categories, four educational levels, and three income levels were used. （附錄一）

Blood, colonoscopy fluid sample will collect for the later analysis.

HLA-DRB1, DQB1, DPB1 genotyping

Genomic DNA for HLA typing will extract from whole blood sample from all participants as manufactural described (Qiagen gentra system, MD, USA). Over two-field resolution of *HLA-DRB1*, *-DQB1*, *-DPB1* allele types will identify by the protocol and primers use sequence-based typing (SBT) amplification. The group-specific SBT method use for amplification exons of *HLA-*

DRB1 (exon 2), -*DQB1* (exon 2, 3), and -*DPB1* (exon 2, 3, 4). The sequencing results will align and identify to IMGT website (https://www.ebi.ac.uk/ipd/imgt/hla/) [59].

Haplotype analysis.

Data analyses will perform in Pypop 0.7.0 [60]. For assessment of Hardy-Weinberg equilibrium (HWE), we use a Chi-square test implemented in Pypop, where observe genotypes are compare to those expect under HWE. The significance level will set to 0.05. Maximum-likelihood haplotype frequencies will estimate in Arlequin, through an expectation–maximization algorithm for unknown gametic phase. Overall linkage disequilibrium (LD) will calculate in Pypop for each pair of loci; 1000 permutations will use for significance-testing and overall LD will measure as W_n, a multiallelic extension of the correlation measure.

Selection of single nucleotide polymorphisms (SNPs)

Criteria for SNP selection. We will select SNPs base on literature search which reported in inflammasome, immune brake, cytokine genes and correlate to disease, especially in CRC and CVD. **Promoter region, 5' or 3' UTR, intron 1, methylation site, splicing site which would correlate to gene functions and tag-SNPs will be the first priority.** Compare to NCBI dbSNP (1000 genome database) and Taiwan Biobank released data (https://taiwanview.twbiobank.org.tw/index). Minor Allele Frequency over 2% will be chosen for further analysis [50].

Sequenom MassARRAY

The SNP genotyping will perform by Sequenom MassARRAY platform with iPLEX gold chemistry (Agena, San Diego, CA). By following the manufacture guide, the specific PCR primer and extension primer sequences are designed with Assay Designer software package (v.4.0). 1 µl of Genomic DNA sample (10 ng/µl) applied to multiplex PCR reaction in 5µl volumes containing 1 unit of Taq polymerase, 500 nmol of each PCR primer mix and 2.5 mM of each dNTP (Agena, PCR accessory and Enzyme kit). Thermocycling was at 94℃ for 4 min followed by 45 cycles of 94℃ for 20 sec, 56℃ for 30 sec and 72℃ for 1 min, then 72℃ for 3min. Unincorporated dNTPs will deactivate using 0.3 U of shrimp alkaline phosphatase. The single base extension reaction using iPLEX enzyme, terminator mix, and extension primer mix followed by 94℃ for 30 sec follow by 40 cycles of 94℃ for 5 sec, and 5 inner cycle of 56℃ for 5 sec and 80℃ for 5 sec, then 72℃ for 3min Agena, iPLEX gold kit). After the addition of a cation exchange resin to remove residual salt from the reactions, 7 µl of the purified primer extension reaction load onto a matrix pad of a SpectroCHIP (Agena). SpectroCHIPs will analyze using a MassARRAY Analyzer 4, and the calling by clustering analysis with TYPER 4.0 software. Genotyping call rates were between 99.0% and 99.5% [61].

MILLIPLEX® MAP Kit on the Bio-Plex® 200 System

The MILLIPLEX® MAP Human Circulating Cancer Biomarker Magnetic Bead Panel 1, 96 well plate assay purchased from EMD Millipore included all the reagents as well as an appropriate plate required by the assay. The procedure was conducted by experienced staff according to the manufacturer's protocol. For washing steps, the Bio-Plex® Pro II wash station was applied. All plates were run on the Bio-Plex® 200 System. Before each assay run, the system was calibrated with the Bio-Plex® calibration kit and validated with the Bio-Plex® validation kit 4.0. Bio-Plex® sheath fluid served as the delivery medium for the samples. Analysis was performed with Bio-Plex® manager 6.1. Within the device settings, 50 events per bead region were defined as minimum criterion. We will test 24 differently coded bead groups, each of which is coated with a specific capture antibody to detect one of the 24 biomarkers which are CEA, AFP, PSA, CA 15-3, CA 19-9, CA 125, CYFRA 21-1, β-HCG, HE4, osteopontin and prolactin, the cell death and angiogenesis markers sFas, sFasL, TRAIL and VEGF as well as the immunological markers IL-6, IL-8, TNFα, TGFα, FGF-2, MIF, leptin, HGF and SCF. The binding of specific analytes begins in the bead mixture suspended with a test sample. Next, a biotinylated detection antibody is introduced and subsequent incubation with streptavidin-phycoerythrin (PE) conjugate is performed to complete the reaction on the microspheres. Finally, the assay is analyzed by the Bio-Plex® 200 system. The procedure will follow the user manuscript.

Analysis of SCFAs in plasma and colonoscopy fluid

Overall, nine analytes were targeted for SCFA analysis. Acetic acid, lactic acid, propionic acid (PA), butyric acid, isobutyric acid, valeric acid (VA), isovaleric acid (iso-VA), pivalic acid (tert-butyl-VA), and caproic acid (CA) were purchased from Wako Pure Chemical Co. For internal standards (IS), PA-d6, BA-d5, VA-d9, and CA-d11 were obtained from Sigma-Aldrich Co. (St. Louis, MO). Triphenylphosphine (TPP), 2,2-dipyridyl disulfide (DPDS), and 2-picolylamine were obtained from Tokyo Kasei Co. (Tokyo, Japan). These stock solutions were adjusted by using methanol. The ultra-performance liquid chromatography (UPLC) system was a Waters Acquity H Class (Waters Co., Milford, MA). A reverse phase analysis was performed via an Acquity UPLC BEH C18 column (1.7 μm, 2.1 °— 100 mm) at 40 °C. The injection volume was 5 μL. The mobile phase consisting of solvent A (0.1% formic acid in water) and solvent B (0.1% formic acid in methanol) was delivered at a flow rate of 0.3 mL/min. The gradient elution was as follows: B% = 2, 2, 35, 45, and 98 (0, 3, 10, 12, and 14 min). A Waters Xevo TQD triple quadrupole mass spectrometer was operated with an electrospray ionization (ESI) source in the positive mode. Useful derivatization of carboxylic acids, mixed SCFAs and IS solutions were diluted by adding methanol.

These solutions were reacted with 2-picolylamine in DPDS and TPP in acetonitrile at 60 °C for 10 min. The reaction mixtures were removed and re-dissolved in 100 μL of methanol/water (80:20, v/v). Finally, the derivatization solutions (5 μL) were analyzed by means of UPLC-ESI-MS/MS. Samples after thawing were added to IS and mixed with equal volumes of methanol and QuEChERS (Supel QuE PSA (EN) 25 mg), vortexed vigorously, and centrifuged at 15,000 rpm for 5 min. The supernatant was then removed, and the remaining residue was re-dissolved in methanol and derivatized by using the process described above for 2-picolylamine. The sample was then analyzed by means of UPLC-ESI/MS/MS.

Microbiota total DNA extraction

1. 250-500 mg centrifuged colonoscopy fluid sample to a ZR BashingBead™ Lysis Tubes (0.1 & 0.5 mm). Add 750 µl ZymoBIOMICS™ Lysis Solution to the tube and cap tightly.
2. Secure in a bead beater fitted with a 2 ml tube holder assembly or Votex-genie 2 and process at maximum speed for ≥ 5 minutes.
3. Centrifuge the ZR BashingBead™ Lysis Tubes (0.1 & 0.5 mm) in a microcentrifuge at ≥ 10,000 x *g* for 1 minute.
4. Transfer up to 400 µl supernatant to the Zymo-Spin™ III-F Filter in a collection tube and centrifuge at 8,000 x *g* for 1 minute. Discard the Zymo-Spin III-F Filter.
5. Add 1,200 µl of ZymoBIOMICS™ DNA Binding Buffer to the filtrate in the Collection Tube from Step 4. Mix well.
6. Transfer 800 µl of the mixture from Step 5 to a Zymo-Spin™ IIC-Z Column in a Collection Tube and centrifuge at 10,000 x *g* for 1 minute.
7. Discard the flow through from the Collection Tube and repeat Step 6.
8. Add 400 µl ZymoBIOMICS™ DNA Wash Buffer 1 to the Zymo-Spin™ IIC-Z Column in a new Collection Tube and centrifuge at 10,000 x *g* for 1 minute. Discard the flow-through.
9. Add 700 µl ZymoBIOMICS™ DNA Wash Buffer 2 to the Zymo-Spin™ IIC-Z Column in a Collection Tube and centrifuge at 10,000 x *g* for 1 minute. Discard the flow-through.
10. Add 200 µl ZymoBIOMICS™ DNA Wash Buffer 2 to the Zymo-Spin™ IIC-Z Column and centrifuge at 10,000 x g for 1 minute.
11. Transfer the Zymo-Spin™ IIC-Z Column to a clean 1.5 ml microcentrifuge tube and add 100 µl (50 ul minimum) ZymoBIOMICS™ DNase/RNase Free Water directly to the column matrix and incubate for 1 minute. Centrifuge at 10,000 x *g* for 1 minute to elute the DNA.
12. Total DNA concentration will detecte by Nanodrop 2000 spectrophotometer.

Next generation DNA sequencing

A two-step PCR protocol for 16S rRNA gene amplification and library preparation was used to perform 16S sequencing on Illumina MiSeq platform. Universal primer pairs 356F (5'CCTACGGGNGGCWGCAG3') and 803R (5'GACTACHVGGGTATCTAATCC3') targeting the V3-V4 region of the bacterial 16S rRNA gene were used for amplification. The two-step PCR protocol used by Ottesen et al.[62] It was employed for 16S rRNA gene amplification and library preparation. In the first step, the target region of 16S rRNA was amplified by using 16S primers with attached overhang adapters (forward primer overhang adapter 5'TCGTCGGCAGCGTCAGATGTGTATAAGAGACAG3', reverse primer overhang adapter 5'GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAG3') compatible with the Illumina Nextera DNA indices. Then, P5/P7 adapters and sample barcodes in the Nextera XT Index Kit (Illumina) were added to the cleaned-up PCR products in the second-round PCR. The final PCR products were cleaned up and sequenced by the Illumina MiSeq platform to generate 2 x 250-bp paired-end reads covering the amplified 16S V3-V4 region.

Taxonomic analysis of 16S sequencing data.

Pair-end reads generated by 16S sequencing were merged by using FLASH v1.2.11 to obtain ~460-bp V3-V4 16S sequences [63]. Merged reads were analyzed with QIIME v1.8.0.[64] First, reads with N bases were removed. Reads containing three or more consecutive low-quality bases ($Q < 20$) were truncated and the length of a trimmed read should be ≥75% of its original length. Reads passing the quality filter were aligned to the Greengenes Database (version Aug. 2013) for chimera check by USEARCH v6.1. Then, UCLUST was applied for OTU clustering at the 97% similarity level [65]. Ribosomal Database Project classifier v2.2 was retrained with the Greengenes Database and utilized to assign taxonomic rank to each representative OTU [66]. CLCbio bacteria OUT analysis suite will be used between different stone type, bile following the user manual.

統計分析

以 STATUS 套裝軟體進行統計分析，將回溯性資料自 2006 年 1 月~2018 年 12 月的資料進行描述性統計分析，將問卷未填寫完整，包含家族疾病史、藥物服用史等排除；大腸清腸前置作業未完整執行，資料不齊全等排除於統計資料收集。符合收錄條件並願意參與研究者的臨床數據進行統計分析。

- 描述性統計分析：
  將分析樣本及分組分析樣本以次數分配及百分比進行本研究對象在性別、各類別的研究變項進行數量及分佈情形描述；並以平均值、標準差、最小值、最大值變異數、範圍、平均數標準誤在各變項研究。
- 獨立樣本 t 檢定（Independent-Samples t-test）：用來檢定組與組在各變項的檢定，各組平均數差異是否達顯著差異之統計方法。
- 卡方檢定（Chi-Square Test）：檢定類別變項的統計檢定方法，本研究對於組與組在相關之類別變項進行分析。
- 邏輯式迴歸（Logistic Regression）：利用邏輯式迴歸分析連續變項在與各組的改變進行分析。

統計分析的部分，我們邀請台灣大學臨床醫學研究所副教授 陳祈玲老師擔任共同主持人，為我們的研究成果進行適切分析與討論。

本研究可能遭遇的困難：

1. 受試者同意書取得不易。健檢中心的受檢者，大部分是對自己的權益及健康狀況較為在意。如此，要取得他們的信任與配合，就必須花費較大的耐心與時間。
2. 腸道菌相的分析相對複雜，有可能所有的菌群變化差異極小，單獨觀察 *Bacteroides*, *Firmicutes*, *Clostridium* 這三種菌群，可能較易有結果產生。
3. 即使在檢驗了上述分子生物標記，如 SCFAs。還是有可能與大腸瘜肉的發生無直接相關。但我們盡力分析所有可能的原因。
4. 如何建立一個有效、即時的分析系統，準確的預測受試者的狀況，是最難的。

對於參與之工作人員，預期可獲之訓練

在臨床上

a. 研究護士、研究助理可習得收案技巧、研究計畫說明、問卷調查整理、受檢者檢體保存方法與規範、受檢者基本釋疑。
b. 新進住院醫師可習得內視鏡、頸動脈超音波操作技巧；幽門螺旋桿菌拭片、大腸瘜肉檢體摘取。

在研究上

a. 助理及醫師們可習得受檢者血液檢體核酸提取、糞便檢體中微生物的分離與核酸提取。生化指標的分析與整理。
b. 統計方法的運用與結果的分析與判斷。
c. 研究論文的闡述與撰寫。

預期完成之研究成果

未來預計將有數篇的研究論文產出；也將參加美國人類遺傳學年會，向全世界展現我們學術研究的成果；在相關的生物標記上的研究成果，如果有顯著的差異，足可作為先期診斷的指標，也會試著申請專利，以利國人。

學術研究、國家發展及其他應用方面預期之貢獻

大腸瘜肉與頸動脈斑塊的病患其腦梗塞及大腸癌的風險會增加。表示會有更多的病患，先後受到這兩種疾病所苦。我們有責任將可能罹患這兩種疾病的受檢者及早篩選出來，給予醫療上的介入，保障國人的健康。在社會上可以保護更多家庭的健康；在經濟上可以減少醫療資源浪費；在學術研究上更了解疾病發展的機轉，促進人類健康。

附錄 1 馬偕紀念醫院健康檢查中心飲食行為與運動習慣問卷

一、基本資料

1.姓名：_____ 2.病歷號碼：_____ 3.性別：□男□女

4.民國_____年_____月_____日 5.身高：_____公分 6.體重：_____公斤

7.腰圍：_____公分 8.臀圍：_____公分

二、日常生活解便習慣（請打ˇ）

9. 在最近三個月當中，排便時是否有費力的情形？

□每次都很費力　□每 3~4 次就有 1 次 □偶爾發生 1 次　□幾乎不曾發生。

10. 在最近三個月當中，排便時是否有糞便呈團塊或硬結的情形？

□每次都呈團塊或硬結　□每 3~4 次就有 1 次　□偶爾發生 1 次　□幾乎不曾發生。

11. 在最近三個月當中，排便時是否有解便不淨感的情形？

□每次都有解便不淨感　□每 3~4 次就有 1 次　□偶爾發生 1 次　□幾乎不曾發生。

12. 在最近三個月當中，排便時是否有肛門阻塞感的情形？

□每次都有肛門阻塞感　□每 3~4 次就有 1 次 □偶爾發生 1 次　□幾乎不曾發生。

13. 在最近三個月當中，排便時是否有需用手挖便或支持骨盆底部的情形？

□每次都需要　□每 3~4 次就有 1 次 □偶爾發生 1 次　□幾乎不曾發生。

14. 在最近三個月當中，每周排便的次數為何？

□每周小於 3 次　□每周 3~5 次 □每周 5~7 次　□每周 7 次以上。

15. 在最近三個月當中，除非使用緩瀉劑，否則很少有軟大便？

□是(需用緩瀉劑)　　□否(不需用緩瀉劑)。

三、飲食習慣（請打ˇ）

16. 多久吃一次高糖分的食物或飲品 (如：糖果、巧克力、汽水、加糖飲料等）？

□每天 2~3 次　□每天 1 次　□2~3 天 1 次　□一星期一次　□不吃或很久一次。

17. 多久吃一次五穀類的食物 (如：飯、麵、麵包等)？

□每天 2~3 次　□每天 1 次　□2~3 天 1 次　□一星期一次　□不吃或很久一次。

18. .一星期喝幾次鮮乳、牛奶或羊奶或乳製品 (如優格、起司)？

□每天２～３次　□每天 1 次　□2~3 天一次　□一星期一次　□不吃或很久一次。

19.多久吃一次高鹽分的食物 (如：臘肉、火腿、熱狗等）？

□每天 2~3 次　□每天 1 次　□2~3 天 1 次　□一星期一次　□不吃或很久一次。

20.多久吃一次高脂肪的食物　(如：煎炸食物、冰淇淋等）？

□每天 2~3 次　□每天 1 次　□2~3 天 1 次　□一星期一次　□不吃或很久一次。

21.多久會吃到肉（豬肉、牛肉、羊肉）雞、鴨、魚（吻仔魚、小魚乾）、海鮮類？

□每天 2~3 次　□每天 1 次　□2~3 天 1 次　□一星期一次　□不吃或很久一次。

22.多久吃一次蔬菜？ □每天 2~3 次　□每天 1 次　□2~3 天一次　□一星期一次

□不吃或很久一次。

23.每天吃多少蔬菜？(一份約 1 個拳頭大小的量)

□超過兩份，_____份　□兩份　□一份　□不到一份。

24.多久吃一次新鮮水果？

□每天 2~3 次　□每天一次　□2~3 天一次　□一星期一次　□不吃或很久吃一次

25.整體而言,覺得自己喜歡的口味？

□很清淡　□很辣　□很鹹　□甜而不油(如:紅豆湯)

□油而不甜(如:炸雞)　□又油又甜(如:巧克力、花生糖)　□普通。

26.一般而言，覺得自己的飲食習慣口味比較偏向？

□很清淡　□很辣　□很鹹　□甜而不油(如:紅豆湯)

□油而不甜(如:炸雞)　□又油又甜(如:巧克力、花生糖)　□普通。

四、運動習慣(請打ˇ)

27.是否有運動習慣？

□每天 2~3 次　□每天一次　□2~3 天一次　□一星期一次　□不運動或很久一次

28.運動的種類(最常運動的種類，至多三種)：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿。

29.每次運動時間多久？＿＿＿＿小時＿＿＿＿分鐘。

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五、申請補助經費：

(一)請將本計畫申請書之第七項(表CM07)、第八項(表CM08)、第九項(表CM09)、第十項(表CM10)、第十一項(表CM11)、第十二項(表CM12)所列費用個別加總後，分別填入「研究人力費」、「耗材、物品、圖書及雜項費用」、「國外學者來臺費用」、「研究設備費」、「國外差旅費-執行國際合作與移地研究」及「國外差旅費-出席國際學術會議」等欄內。

(二)管理費為申請機構配合執行本計畫所需之費用，其計算方式係依本部規定核給補助管理費之項目費用總和及各申請機構管理費補助比例計算後直接產生，計畫主持人不須填寫「管理費」欄。

(三)「貴重儀器中心使用額度」係將第十三項(表CM13)所列使用費用合計數填入。

(四)請依各年度申請博士後研究之名額填入下表，如於申請時一併提出「補助延攬博士後研究(含大陸)員額/人才進用申請書」（表CIF2101、CIF2102），若計畫核定僅核定名額者應於提出合適人選後，另依據本部「補助延攬客座科技人才作業要點」規定向本部提出進用申請，經審查通過後，始得進用該名博士後研究。

(五)申請機構或其他單位（含產業界）提供之配合項目，請檢附相關證明文件。

金額單位：新臺幣元

補助項目 \ 執行年次		第一年（108年8月～109年7月）	第二年（109年8月～110年7月）	第三年	第四年	第五年
業務費		**1,239,667**	**1,079,440**			
研究人力費		564,567	579,840			
耗材、物品、圖書及雜項費用		675,100	499,600			
國外學者來臺費用		0	0			
研究設備費		**0**	**0**			
國外差旅費		**120,000**	**120,000**			
執行國際合作與移地研究		0	0			
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貴重儀器中心使用額度		0	0			
博士後研究	國內、外地區	共 0 名	共 0 名	共 名	共 名	共 名
	大陸地區	共 0 名	共 0 名	共 名	共 名	共 名

申請機構或其他單位（含產業界）提供之配合項目（無配合補助項目者免填）

配合單位名稱	配合補助項目	配合補助金額	配合年次	證明文件

六、主要研究人力：

(一)請依照「主持人」、「共同主持人」、「協同研究人員」及「博士後研究」等類別之順序分別填寫。

類 別	姓名	服務機構/系所	職稱	在本研究計畫內擔任之具體工作性質、項目及範圍	＊每週平均投入工作時數比率(%)
主持人	胡光濬	台灣基督長老教會馬偕醫療財團法人馬偕紀念醫院內科	主治醫師(滿二年)	計畫發想、臨床確診、統計收案、研究結果討論與撰寫、期刊發表	50%
共同主持人	楊鴻偉	台灣基督長老教會馬偕醫療財團法人馬偕紀念醫院醫學研究部	助研究員	計劃收案整理、新穎生物標記分析、腸道菌相研究結果討論與報告撰寫	50%
共同主持人	施壽全	台灣基督長老教會馬偕醫療財團法人馬偕紀念醫院內科	主治醫師	協助臨床收案、研究結果討論與撰寫	30%
共同主持人	陳祈玲	國立臺灣大學醫學院臨床醫學研究所	副教授	研究結果之統計分析、解釋及討論	20%

※ 註：每週平均投入工作時數比率係填寫每人每週平均投入本計畫工作時數佔其每週全部工作時間之比率，以百分比表示（例如：50%即表示該研究人員每週投入本計畫研究工作之時數佔其每週全部工時之百分五十）。

(二)如申請博士後研究，請另填表CIF2101及CIF2102(若已有人選者，請務必填註人選姓名，並將其個人資料表(表C301～表C303)併同本計畫書送本部)。

七、研究人力費：

(一)凡執行計畫所需助理人員費用，均得依預估研究人力（專任助理、兼任助理及臨時工）需求填寫，並請述明該助理人員在本計畫內擔任之具體內容、性質、項目及範圍，以利審查。

(二)約用專任助理，請依其於專題研究計畫負責之工作內容，所應具備之專業技能、獨立作業能力、預期績效表現及相關學經歷年資等條件，綜合考量敘薪，並檢附各機構自訂之薪資支給依據，以為本部核定聘用助理經費之參考。

(三)請分年列述。

第 1 年　　金額單位：新臺幣元

類別	金額	請敘明在本計畫內擔任之具體內容、性質、項目及範圍 （如約用專任助理，請簡述其於計畫內所應具備之專業技能、獨立作業能力、預期績效表現及相關學經歷年資等條件）
專任助理	564,567	協助個案收集、檢體統計整理、研究文獻查詢整理、研究結果彙整、生物標記檢驗 564,567元(含月支費用、年終獎金、勞健保費雇主負擔部分、勞工退休金雇主負擔部分) x 1名
合計	564,567	

第 2 年　　金額單位：新臺幣元

類別	金額	請敘明在本計畫內擔任之具體內容、性質、項目及範圍 （如約用專任助理，請簡述其於計畫內所應具備之專業技能、獨立作業能力、預期績效表現及相關學經歷年資等條件）
專任助理	579,840	協助個案收集、檢體統計整理、研究文獻查詢整理、研究結果彙整、新穎生物標記檢驗 579,840元(含月支費用、年終獎金、勞健保費雇主負擔部分、勞工退休金雇主負擔部分) x 1名
合計	579,840	

八、耗材、物品、圖書及雜項費用：

(一)凡執行研究計畫所需之耗材、物品(非屬研究設備者)、圖書及雜項費用，均可填入本表內。
(二)說明欄請就該項目之規格、用途等相關資料詳細填寫，以利審查。
(三)若申請單位有配合款，請於備註欄註明。
(四)請分年列述。

第 1 年　　金額單位：新臺幣元

項目名稱	說明	單位	數量	單價	金額	備註
論文發表費	學術研究成果發表	筆	1	50,000	50,000	
審查費	人體研究倫理審查費	筆	1	10,500	10,500	
消耗性器材	採血管	盒	2	1,000	2,000	
消耗性器材	MILLIPLEX(®) MAP Human Circulating Cancer Biomarker Magnetic Bead Panel	組	4	30,000	120,000	
消耗性器材	SCFAs assay kit	組	4	15,000	60,000	
消耗性器材	Sequenom MassArray assay Suit	批	1	40,000	40,000	
消耗性器材	微量離心管	箱	2	3,200	6,400	
消耗性器材	一般常用化學藥劑(如 Alcohol, salt,chemicals, ammonium acetate, formic acid)	批	1	15,000	15,000	
消耗性器材	1000 ul tip 實驗耗材	包	12	600	7,200	
消耗性器材	單用式微量吸管	箱	1	4,000	4,000	
消耗性器材	HLA-B genotyping	件	100	900	90,000	
消耗性器材	HLA-DQB genotyping	件	100	900	90,000	
消耗性器材	HLA-DRB genotyping	件	100	900	90,000	
消耗性器材	HLA-DPB genotyping	件	100	900	90,000	
合　　計					675,100	

第 2 年　　金額單位：新臺幣元

項目名稱	說明	單位	數量	單價	金額	備註
論文發表費	研究結果論文發表	筆	1	50,000	50,000	
消耗性器材	採血管	盒	2	1,000	2,000	
消耗性器材	微量離心管	箱	2	3,200	6,400	
消耗性器材	一般常用化學藥劑(如	批	1	10,000	10,000	

	Alcohol, salt, chemicals, ammonium acetate, formic acid)					
消耗性器材	1000 ul tip 實驗耗材	包	12	600	7,200	
消耗性器材	核酸萃取試藥套組 ZymoBiomics DNA miniprep kit	組	2	12,000	24,000	
消耗性器材	Next generation DNA sequencing for 16S ribosomal RNA	件	100	4,000	400,000	
合　　計					499,600	

十二、國外差旅費-出席國際學術會議：

(一)計畫主持人及參與研究計畫之相關人員參加國際學術會議得申請本項經費。
(二)請詳述預定參加國際學術會議之性質、預估經費、天數及地點。
(三)機票費、生活費及其他費用之標準，請依照行政院頒布之「國外出差旅費報支要點」規定填列(網址https://law.dgbas.gov.tw/LawContent.aspx?id=FL017584)。
(四)請詳述計畫主持人近三年參加國外舉辦之國際學術會議論文之發表情形。(包括會議名稱、時間、地點、發表之論文題目、補助機構，及後續收錄於期刊或專書之名稱、卷號、頁數、出版日期)
(五)請分年列述。

第 1 年　　金額單位：新臺幣元

出席國際學術會議			
博士生人數	共 1 名	金　額	120,000
費用說明	2019 美國人類遺傳學會年會 學術會議性質：人類遺傳、疾病、醫療新知研討會 預估經費：航班機票、食宿、交通、註冊費、入會費，預計120000元。 舉辦日期：2019/10/15-10/19，加航班時程約八天。 舉辦地點：美國休士頓		
近三年論文發表情形	1: Lin JL, Sung KT, Su CH, Chou TH, Lo CI, Tsai JP, Chang SC, Lai YH, Hu KC, Liu CY, Yun CH, Hung CL*, Yeh HI, Lam CSP. Cardiac Structural Remodeling, Longitudinal Systolic Strain, and Torsional Mechanics in Lean and Nonlean Dysglycemic Chinese Adults. Circ Cardiovasc Imaging. 2018 May;11(5):e007047. 2: Kuo YC, Shih SC, Yu LY, Wu MS, Su TH, Liu CJ, Hu KC*. Age and gender may be the key points in hyperglycemic patients with Helicobacter pylori infection combined colorectal adenoma. Helicobacter. 2018 Apr;23(2):e12473. 3: Hu KC, Wu MS, Chu CH, Wang HY, Lin SC, Po HL, Bair MJ, Liu CC, Su TH, Chen CL, Liu CJ, Shih SC*. Hyperglycemia combined Helicobacter pylori infection increases risk of synchronous colorectal adenoma and carotid artery plaque. Oncotarget. 2017 Oct 26;8(65):108655-108664. 4: Hu KC, Wu MS, Chu CH, Wang HY, Lin SC, Liu SC, Liu CC, Su TH, Chen CL, Liu CJ, Shih SC*. Synergistic Effect of Hyperglycemia and Helicobacterpylori Infection Status on Colorectal Adenoma Risk. J Clin Endocrinol Metab. 2017 Aug 1;102(8):2744-2750. 5: Yen CH, Wang KT, Lee PY, Liu CC, Hsieh YC, Kuo JY, Bulwer BE, Hung CL*, Chang SC, Shih SC, Hu KC, Yeh HI, Lam CSP. Gender-differences in the associations between circulating creatine kinase, blood pressure, body mass and non-alcoholic fatty liver disease in asymptomatic asians. PLoS One. 2017 Jun 30;12(6):e0179898. 6: Hu KC, Chu CH, Wang HY, Chang WH, Lin SC, Liu CC, Liao WC, Liu CJ, Wu MS, Shih SC*. How Does Aging Affect Presentation and		

	Management of Biliary Stones? J Am Geriatr Soc. 2016 Nov;64(11):2330-2335. 7: Lin CC, Bair MJ, Chen CJ, Lee KH, Chen MJ, Liu CY, Chang CW, Hu KC, Liou TC, Lin SC, Wang HY, Chu CH, Shih SC, Wang TE. Off-treatment efficacy of 3-year nucleos(t)ide analogues in chronic hepatitis B patients. Kaohsiung J Med Sci. 2016 Jan;32(1):10-5.

第 2 年　　金額單位：新臺幣元

出席國際學術會議			
博士生人數	共 1 名	金　額	120,000
費用說明	2020 美國人類遺傳學會年會 學術會議性質：人類遺傳、疾病、醫療新知研討會 預估經費：航班機票、食宿、交通、註冊費、入會費，預計120000元。 舉辦日期：2020/10/27-10/31，航班時程約八天。 舉辦地點：美國聖地牙哥		
近三年論文發表情形	1: Lin JL, Sung KT, Su CH, Chou TH, Lo CI, Tsai JP, Chang SC, Lai YH, Hu KC, Liu CY, Yun CH, Hung CL*, Yeh HI, Lam CSP. Cardiac Structural Remodeling, Longitudinal Systolic Strain, and Torsional Mechanics in Lean and Nonlean Dysglycemic Chinese Adults. Circ Cardiovasc Imaging. 2018 May;11(5):e007047. 2: Kuo YC, Shih SC, Yu LY, Wu MS, Su TH, Liu CJ, Hu KC*. Age and gender may be the key points in hyperglycemic patients with Helicobacter pylori infection combined colorectal adenoma. Helicobacter. 2018 Apr;23(2):e12473. 3: Hu KC, Wu MS, Chu CH, Wang HY, Lin SC, Po HL, Bair MJ, Liu CC, Su TH, Chen CL, Liu CJ, Shih SC*. Hyperglycemia combined Helicobacter pylori infection increases risk of synchronous colorectal adenoma and carotid artery plaque. Oncotarget. 2017 Oct 26;8(65):108655-108664. 4: Hu KC, Wu MS, Chu CH, Wang HY, Lin SC, Liu SC, Liu CC, Su TH, Chen CL, Liu CJ, Shih SC*. Synergistic Effect of Hyperglycemia and Helicobacterpylori Infection Status on Colorectal Adenoma Risk. J Clin Endocrinol Metab. 2017 Aug 1;102(8):2744-2750. 5: Yen CH, Wang KT, Lee PY, Liu CC, Hsieh YC, Kuo JY, Bulwer BE, Hung CL*, Chang SC, Shih SC, Hu KC, Yeh HI, Lam CSP. Gender-differences in the associations between circulating creatine kinase, blood pressure, body mass and non-alcoholic fatty liver disease in asymptomatic asians. PLoS One. 2017 Jun 30;12(6):e0179898. 6: Hu KC, Chu CH, Wang HY, Chang WH, Lin SC, Liu CC, Liao WC, Liu CJ, Wu MS, Shih SC*. How Does Aging Affect Presentation and Management of Biliary Stones? J Am Geriatr Soc. 2016 Nov;64(11):2330-2335.		

	7: Lin CC, Bair MJ, Chen CJ, Lee KH, Chen MJ, Liu CY, Chang CW, Hu KC, Liou TC, Lin SC, Wang HY, Chu CH, Shih SC, Wang TE. Off-treatment efficacy of 3-year nucleos(t)ide analogues in chronic hepatitis B patients. Kaohsiung J Med Sci. 2016 Jan;32(1):10-5.

十四、近三年內執行之研究計畫

（請務必填寫近三年所有研究計畫，不限執行本部計畫）

計畫名稱 （本部補助者請註明編號）	計畫內擔任之工作	起迄年月	補助或委託機構	執行情形	經費總額
慢性B型肝炎併肝硬化患者接受抗病毒藥物治療之追蹤研究-延伸計畫	共同主持人	2016/09/01～2019/08/31	台大,榮總,長庚,馬偕等醫學中心胃腸肝膽內科	執行中	200,000
合　　計					200,000

十六、科技部補助研究計畫涉及臨床試驗之性別分析檢核表：

研究人員 姓　　名	胡光濬		
任職機關 系　　所	馬偕紀念醫院胃腸肝膽科	職　　稱	主治醫師
計畫名稱	大腸腺瘤性瘜肉合併頸動脈內皮斑塊形成之新穎評估因子探究		

說明：
本年度專題研究計畫若涉及臨床試驗，應填寫「性別分析檢核表」，填寫後請以附件上傳申請系統。

項次	項目	說明	備註
1	本計畫涉及臨床試驗之研究對象。	1. 說明後有意願參加之受試者(年齡20-75歲)。 2. 收錄2006年01月01日～2018年12月31日於馬偕紀康檢查中心同時接受生理檢驗、無痛大腸鏡、頸動脈超音波分析的健康受檢者(年齡20-75歲)。 3. 病例回溯符合條件之個案 4. 16MMHIS066之去連結檢體 5. 台灣人體生物資料庫所釋出之資訊	
2	本計畫預計之收案件數及其性別比例。	預計新收案200人，男女各佔50%。	
3	本計畫如未進行性別分析(進行性別統計分析及差異評估)，請說明理由。若已有文獻證明無性別差異，請提供相關資料。	我們先前的研究統計顯示男性罹患幽門螺旋桿菌合併高血糖產生大腸腺瘤性瘜肉與頸動脈內皮斑塊的機率高於女性。因此，本計劃將會進行性別差異分析。	

馬偕紀念醫院人體研究倫理審查委員會通知

Dear 胡光濬主持人您好：

本院人體研究倫理審查委員會已於2018年12月18日茲收到您提出之「大腸腺瘤性瘜肉合併頸動脈內皮斑塊形成之新穎評估因子探究」計畫案申請(本院編號：18MMHIS185)，特此函知。

馬偕紀念醫院人體研究倫理審查委員會

2018年12月18日