原住民族委員會 110 年度 0000 補助案

成果報告書

執行單位：　個人　(台灣大學生物科技研究所)

計畫名稱：　至西班牙巴塞隆納參加 Gordon Research Conference Neurobiology of Brain Disorder 研討會並發表研究成果(海報)

結案日期：111/09/07

活動成果報告書格式：

（請用 A4 影印紙繕打）

Gordon Research Conference 辦理「Neurodegenerative Disease: From Molecular Mechanisms to Potential Therapies & Fundamental Mechanisms Leading to Novel Therapeutics and Biomarkers for Neurodegenerative Disease」成果報告書

<table>
<tr><td>壹、前言</td><td colspan="2">2022年戈登腦疾病神經生物學會議將匯集基礎、臨床和轉化研究領域的領導者，討論他們的最新發現和新概念。受邀演講者代表了廣泛的科學學科，包括遺傳學、基因組學、系統生物學、細胞生物學、細胞和動物疾病建模、生物標誌物發現和治療開發。</td></tr>
<tr><td rowspan="7">貳、活動執形</td><td colspan="2">一、名稱： Gordon Research Conference 的 Neurobiology of Brain Disorder</td></tr>
<tr><td colspan="2">二、地點：巴賽隆納，西班牙</td></tr>
<tr><td colspan="2">三、參加人數：200 餘人</td></tr>
<tr><td rowspan="4">四、經費支出概況</td><td>1.原計畫金額： 新臺幣 105,330 元</td></tr>
<tr><td>2.實際支出金額：新臺幣 105,330 元</td></tr>
<tr><td>3.經費分攤情形（% ）：
機票費 NT 57,024 (54.1%)
註冊費（含食宿）NT 48,306 (45.9%)</td></tr>
<tr><td>4. 原計畫經費與實際支出經費之落差說明：（分點詳述）
無落差</td></tr>
<tr><td>五、計畫執行效益、特色及影響：</td><td>（分點詳述）
● 為研究生提供一個展示手上的工作並與該領域的領導者進行非正式互動的平台
● 讓自己的研究有被國際學者看見的機會（有助於確定研究方向、精進研究品質） 1 建立國際人脈（藉此結交同一領域研究社群的朋友） 1 提高語言能力的動機</td></tr>
</table>

	六、大眾傳播媒體及部落	1. 與會的研究生們也有一些是當地的原住民，對於當地的文化以及生活背景有熱絡交流。 2. 無新聞媒體採訪（附上參與證書）

	內部反應或大眾評價：	
參、自我優劣鑑	一、優點：(分點詳述) 1. 能和各國實驗室的人員包含 PhD student, Postdoc, 以及 PI 有許多研究、實驗上的交流 2. 快速適應外國的環境以及語言	
	二、缺點：(分點詳述) 1. 一開始對於主動表示研究上的看法有點膽怯，但後幾舔逐漸可以找到自己舒服的討論方式	
肆、討論與建議	一、 與原訂計畫之落差： 計畫核定經費金額比預期的少	
	二、有無製作紀錄供作未來之參考？ 有整理會議筆記 2022 GRC，如附在成果報告書之後	

	二、 改進意見：(分點詳述) 1. 投票制度落實於主席選擇、會議地點上面：GRC 的 Neurobiology of Brain Disorder 會採用投票的方式選出下一屆的主席，以及適合辦理的地點，候選的地點則是由與會者自由提出、介紹預計地點及效益如何，我發現各個國家都很熱烈提出以及推薦自己當主席，最後的決定下一屆的主席是由 Michael 老師負責，舉辦地點也是在歐洲舉辦，我覺得台灣或許在舉辦研討會在主席選擇以及地點也可以採取這種方式。 2. 完善的註冊模式：此次的會議的註冊系統可以讓我們知道所有與會人員的聯絡方式（包含 email 以及聯絡電話)，我覺得這部分不錯，因為有助於訊息往來、促進國際合作；另外每個與會人員都會拿到一組 photo ID 之後就可以用這個 ID 登入下載會期當中的照片，我覺得這個設蠻貼心的，或許之後在台灣舉辦的研討會與可以參考類似做法。 3. 研討會之於結合當地的人文特色：研討會固然重要，但主辦方也知道來到外地觀光以及結合當地的問話或許也是國際研討會本身應該具備的，因此 GRC 的研討會也不例外，在吃完午餐到下午四點半 poster session 之前，每天都有不一樣的觀光行程，例如：巴賽隆那市中心觀光巴士、參觀葡萄酒莊園、參觀歷史遺跡，讓充實的研討會裡面也可以享受在地的人文風情，購買相關產品、伴手禮。在我國發展觀光產業的同時，借鏡國外的做法，結合當地的故事性以及主題性或許能提升台灣在國際研討會上面增加外國人來台意願。
伍、結論與建議事項	● 此次的出國研討會，對於腦神經科學領域有了新的體驗，更實實在在的認識一群頂尖的科學家們，台灣的研究不容小覷，綜觀世界上的神經科學研究，我們其實可以有更多實質性的國際交流合作，有助於對於解開許多疾病分子機制上往前邁進！ ● 對於主旨想要傳遞一份自然科學的魅力給予部落的小孩子的種子依然在我心中，倘若有機會也希望原民會可以邀請我分享走上自然科學這條路的契機。 ● 謝謝原民會補助我這趟出國行。雖然仍有部分自費支出，但也讓我可以減輕一些出國壓力。

註：成果報告書附件（必附）	一、原活動計畫書 二、本會核定函 三、活動相片（活動每一流程至少 2 張，總數不得少於 12 張，並以電腦打字加註說明） 四、DVD（計畫書有列攝影費用者須附） 五、參加人員名冊（並註明族別） 六、文宣品、報導剪報影本

一、 參加會議經過 Conference Introduction

筆者此次獲科技部補助參加於 GRC 舉辦之 Neurobiology of Bain disorder，會議地點為西班牙巴賽隆納郊區，會議自民國 111 年 08 月 06 日至 08 月 12 日，為期七天。這也是筆者第一次單獨自己出國參與國際研討會於 08 月 04 日晚間由桃園機場起飛抵達土耳其伊斯坦堡機場，08 月 05 日凌晨在飛往西班牙巴賽隆納機場，在當天早上下榻到飯店後休息一天便開始為期一個禮拜的研討會。此次研討會聚集來自世界各地在腦神經科學領域的權威（有些教授是 Nature 的第一作者）、來自歐、美籍亞洲地區，歐美人數比例最多。

整個會期主要分成兩個階段：第一個階段是 Gordon Research Seminar (GRS)從星期六(08/06) 到星期日 (08/07)，題目是：Neurodegenerative Disease: From Molecular Mechanisms to Potential Therapies，主要是給研究生、博士後以及年輕學者（大約 70 餘人）提供機會，討論他們關於遺傳學、免疫機制、RNA 代謝、溶酶體生物學、自噬、表觀遺傳變化、細胞內機制、蛋白質加工和細胞間相互作用等主題的基礎和轉化研究，當中也有海報時間 (poster session)促進更多學術上的交流、分享，且會由博士後、抑或年輕學者之經驗分享，十足珍貴。

第二個階段就是 GRC 大會時間 (08/08~08/12)，主題是 Fundamental Mechanisms Leading to Novel Therapeutics and Biomarkers for Neurodegenerative Disease，參與人數 200 餘人（包含 GRS 人數），大會時間進來的多為各個實驗室的 PI、博

士後、研究學者（公司） 藉著匯集基礎、臨床和轉化研究領域的領導者，討論他們的最新發現和新概念（多為 unpublished data）。 受邀演講者代表了廣泛的科學學科，包括遺傳學、基因組學、系統生物學、細胞生物學、細胞和動物疾病建模、生物標誌物發現和治療開發。 最重要的是會議還為初級科學家和研究生提供一個展示他們的工作並與該領域的領導者進行非正式互動的平台（或許可以稱作 bar time 時間聊聊）。 本次會議論文發表分為論文宣讀及論文海報展示兩種方式，其中論文宣讀共有 61 場次(含主題演講 9 場)（GRS+GRC），海報展示則有 207 篇，所涵蓋之主題如下: (1) Intercellular Communication in Alzheimer's Disease ; (2) Identifying and Characterizing Neurodegeneration; (3) Innovations in Therapeutics; (4) Neuronal Excitability and Neurodegeneration; (5) Development of Novel Blood-Based Biomarkers for Neurodegenerative Disease; (6) Genetic and Genomic Approaches to Neurodegenerative Disease; (7) Epigenetics of Neurodegenerative Disease; (8) Frontotemporal Dementia and ALS: Mechanisms; (9) Parkinson's Disease: Mechanisms; (10) Alzheimer's Disease: Mechanisms; (11) Tauopathies: Mechanisms and Biomarkers; (12) Biomarkers: Diagnoses and Therapeutics; (13) Therapeutics Approaches。筆者的海報時間是星期日下午以及星期三下午，除於會場聆聽有興趣之主題演說及解說與觀摩海報外，筆者也有去認識巴賽隆納城市。本次會議期間與會者從研究生到各個領域的巨擘均熱烈發言討論，收穫不少。本人於 08 月 12 日巴賽隆納搭機，並於伊斯坦堡機場轉機，於 13 日返抵桃園國際機場，結束此次研討會行程。

二、 與會心得 Feedback after Attending Conference(with Photos)

1. 此次為第一次參與國際級的研討會，能夠和世界上腦神經科學領域的人們聚在一起心裡實在激動，對於只是碩士生的我而言是很大的自我肯定，絕大多數與會者都是博士生、博士後以及各個實驗室的老闆，這個陣容為龐大，但也正因為如此提醒我自己可以汲取更多在這個領域的新知，在會場言演講者們的分享內容裡最常聽大的就是：「這是尚

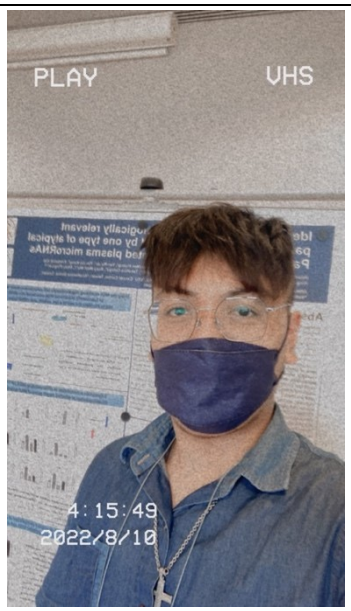
未發表的數據！」怎麼可以不好好的記錄下來在每一個數據、故事中的科學家們的點點滴滴，尤其是在我自己的領域帕金森氏以及類帕金森氏中的權威們也不吝於分享自己在發現這些甜美研究成過之秘辛，其中比利時 VIB-KULeuven Center for Brain & Disease Research 的博後所發表之"Multi-omics Targetome Profiling of MicroRNA-132 for Therapeutic Targeting in AD"和我一樣從事 miRNA 的相關研究，在 poster session 時段有很好的交流給予我許多實驗建議，甚是感恩，最後大多實驗室也都蠻歡迎新血加入，讓我也在這次國外研討會交流下對於外國做研究有些憧憬。

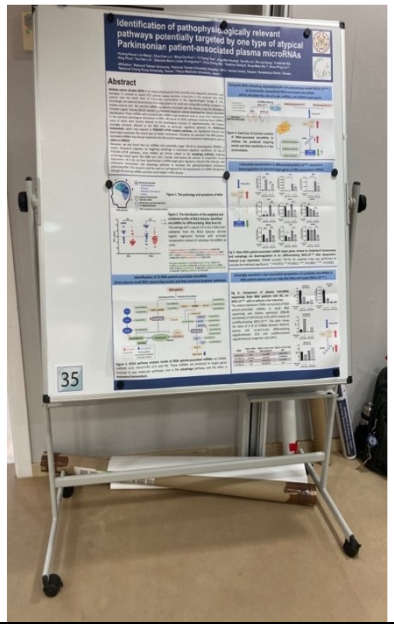
2. 在 poster session 時給我蠻大的衝擊，原來熱烈的討論各式各樣的研究是經常如此的，在國外相較於在國內這部分的差異明顯，雖然短短的一個半小時，從頭到我都有人來和我討論我的研究內容，在邏輯思考、研究架構給予我很大的啟發，其中最讓我印象深刻的是和美國國家衛生研究院 (NIH) 的 Michael 老師互動：在 Michael 老師來之前，Aaron 老師其實就也先來看我的海報，Aaron 老師今年二月才在 Nature Article 上面發表（為第一作者），能夠讓 Aaron 老師對我的研究感動興趣真的很感激，Michael 老師其實也就是 Aaron 老師建議來看我的海報的，在漢 Michael 老師討論才發現原本自己覺得沒什麼的結果是繼上卻可能帶來新的發現，前人所累積的經驗讓我深感佩服，我也在這次意猶未盡的討論之後寫信給 Michael 老師和老師有更多的研究、過往在該領域經驗的討論，著實啟發我對於探索未知事物的熱情。

3. 研究自始自終都是為了提升人類的生活福祉，因此國際的研究交流可更使得這一個目標較容易達成，因此我了解到結合國際視野於自己的研究中的重要性，有歧視我們針對的是腦神經疾病，對於了解並生理，才更有助於發展出更精準的治療模式，如此重大的會議國內僅有筆者參加，而無產業界以及學界人士參與，實在可惜。

活動相片：

註：剛抵達此次研討會舉行及住宿飯店：GRAN HOTEL REYDON JAIME	註：研討會下午 free time 的自由行程
註：和 Berni 教授合照（背景是 PRBB 旁邊的海灘）	註：和 Berni 教授合照（我的指導老師在劍橋時同學）背景是 PRBB building

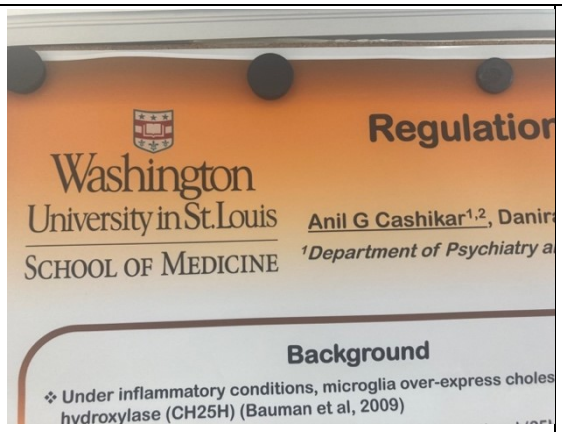




註：和我的海報自拍

註：我的海報

註：GRC 大會合照



註：來自世界各國學長姐海報一隅	註：GRAN HOTEL REYDON JAIME 風景
註：報到時的名牌	註：註：加泰羅尼亞廣場一隅
註：與大會 GRS&GRC 自拍	

GRC 2022 Note

Henne Holstege (Vrei University of Amsterdam, The Netherlands)

"WGS Sequencing in AD"

What is the gene in Alzheimer's disease?

Rare variant in SORL1 TREM2 ABCA7

Aims: Identification of genes in which rare genetic variants associated with AD

- One server, one pipeline 25,982 genomes (Batch effects)
  Solution
  - Sample quality control
  - Variant quality control
  - Variant selection
  - Inflation:1.046 is low tell us we remove the batch effect
  - Discover: stage1
  - Confirmation: stage2
  - Meta analysis stage 1&2
- Summary and conclusion: Identify two new genes in AD
- ATP8B4 and ABCA1

If we can't bring the data to the researcher, bring the research to the data.

Publication: MedRxiv

Sonja Scholz (National Institutes of Health, United States)

Defining the Genetic Architecture of Lewy Body Dementia (LBD)

- Lewy body disease: Parkinson's disease and LBD
- LBD genome sequencing initiative
  - Disease-associated genetic variation
  - LBD genome resource
- GWAS identified 5 loci: GBA, BIN1, TMEM175, SNCA, APOED

- LBD patients have higher risk than AD and PD
- GBA is a plemophic risk locus for LBD
- Pure DLB with higher GBA-positive
- Clinicopathological characters: SNCA- and TDP-43- positive
- Drug discovery by combing epidemiological and genomic analyses
    - Cardiovascular disease management drug can reduce the risk of LBD

Peter Heutink (German Center for Neurodegenerative Diseases (DZNE) Tübingen, Germany)

"Increased Sensitivity of MAPT H1/H1 iNeurons to Mild Chronic Oxidative Stress"

- 1.5-Mb of high linkage disequilibrium on chromosome 17q21.31
- H1-H2 haplotypes
- MAPT 17q21.31 locus harbors important risk alleles for a series of human phenotypes
- Long term omission antioxidant from culture medium (B-27 supplement minus AO) of SMNPCs showed reduced viability of H1/H1 during differentiating into neurons compared H2/H2
- Mild Chronic Oxidative Stress (MCOS)
- Does response curve of 87 hits
- Pathway analysis of verified hits
- Enrichment for compound s associated with ferroptosis
- Reported differences H1 vs H2
- NRF2 is a master regulator oxidative stress response and binds to an antioxidant response element (ARE) on chromosome 17q21 upstream of MAPT

Hemali Phatnani (Columbia University/New York Genome Center, United States)

"Using Spatial Genomics to Study the Central Nervous System in Health and Disease

- ALS-FTD: IPS cell, postmortem tissues
- Spatially encoded RNAseq
    - Histology

    - Permeabilization
    - Reverse transcription
    - Library-Prep
    - Sequencing
    - Ventral horn
    - Hierarchical generative probabilistic model for ST analysis (Splotch)
- ALS-STNYgenome
- Summary
    - Mouse model to build ST model
- TDP-43 pathology in ALS-FTD
- How to TDP-43 aggregates at surrounding cell
- Iterative indirect IF imaging (staining elution, imaging)(4i)
- Open source approach to automation of 4i protocol (open source)
- Pyseq 2500
- To build 3D age across the same region profiling

John Tuddenham (Columbia University, United States)

"Developing and Translating a Transcriptomic Taxonomy of Live Human Microglia Across Aging and Neurologic Diseases"

- Human microheterogeneity at single cell resolution
- 12 microglia subset with distinct function/disease association
- Recapitulation of microglia phenotypes in vitro
- Camptothecin induced upregulation of cluster 10 genes
- Paper name: A cross-disease human microglia framework identifies disease-enriched subsets and tool compounds for microglia polarization

Emmy Li (University of California, San Francisco, United States)

"CRISPRi-based genetic screens in iPSC-derived 3D neuron-astrocyte-microglia iAssembloids"

- 3D neuronal cultures with glia expands upon previous screens
- Build new model
- Elucidate the effect of glia
- 6 neurons 2 astrocytes and 1 microglia

- How the presence of glia affects neuronal survival
- Differential hits in iAssembloids vs monoculture are related to neuronal activity
- Which has the most dramatic effect on survival
- What is driving increase in GSK3B?
- Excess glutamate can increase ROS
- GSK3B activity affect NRF2 localization!

Jack Humphrey (Icahn School of Medicine at Mount Sinai, United States)

"Long-read RNA-seq of Human Microglia Reveals Novel Isoforms and Elucidates Alzheimer's-Associated Genetic Regulation of Splicing"

- Functional genomics can identify new risk genes and implicate specific cell types in neurodegeneration
- Microglia Genomics Atlas(MiGA)
- Long-reads RNA-seq
- Figure made with BioRender
- Expression QTL (eQTL)- Genotype associates with total gene expression
- *SIGLEC11* has a novel isoform colocalizing with AD GWAS

Benjamin Wolozin (Boston University School of Medicine, United States)

"Epitranscriptional Regulation of N6-methylated RNA in AD"

- Unbiased proteomic identifies HNRNPA2B1 functions as m6A reader the m6A life cycle: Writers, Readers, and Erasers
- hnRNPa2b1 and m6A colocalize with tau pathology in vivo
- Human brain
- The increased level of m6A in tauopathy are reflected by
- DEG m6ARNAseq, accumulation of m6A is a feature of other NDD including ALS
- TDP-43 target are enriched for m6A
- oTau forms a complex with HNRNPA2B1 and m6A

Sangram Sisodia (univ of chicago, United States)

"Modulation of AD-Type Neuropathology by the Gut Microbiome"

- risk factor: chromosome 10: Bin1, ABCA7, ApoJ, CD33, PECALM
- Emerging evidence now suggest gut microbial diversity can regulate brain function through control of host
- All disease begins in the gut!!
- Germ free mice
- Transcriptomic analysis of cortical tissue
- TgFMT into ABX-male mice restores CD-69ir microglia
- Paper name: Sexual dimorphism in predisposition to AD

Leslie Thompson (University of California, Irvine, United States)

"Molecular Pathogenesis in Huntington's Disease"

- Epigenetic in HD systems
- Single nuclei RNAseq reveals cell type specific gene expression change in HC mice and human brain
- PRKCE is an upstream regulator of OL
- TDP43 binding target are enriching in m6A sites
- Mis localization of TDP-43 in HD mouse and human brain

Michael Heneka (Université du Luxembourg, Luxembourg)

"Microglia Derived Tunneling Nanotubes Ensure Functional and Structural Integrity of Neurons"

- Intraneuronal a-syn.
- A-syn transfer from neurons to glia
- A-syn transfer require physical contact
- Microglia from TNTs with neurons
- TNTs allows for transfer of a-syn-/tau aggregates
- PhD students hiring

Dorothee Dormann (Johannes Gutenberg University (JGU) and Institute of Molecular Biology (IMB) Mainz, Germany)

"Aberrant Phase Transitions of ALS/FTD-Linked RNA-Binding Proteins – Control Mechanisms and Functional Consequences"

- Early working model: mechanism of RBP mis localization and aggregation
- Physiological and pathological phase separation: membrane-less organelles, stress granules
  - Liquid to liquid (state transition), suppressing factor? Promoting factor?
  - Liquid to solid
- Kinase overexpression (increase aggregation of TDP-43)
- Phosphomimetic substitution in TDP-43 reduce aggregation (more liquid-like and dynamic)
- TDP-43 phosphorylation follows insolubility

Jeffrey Rothstein (Johns Hopkins University, United States)

"Nuclear Pore Complex Dysfunction in ALS/Dementia: Disease Initiation, Propagation and Downstream Mitigation of TDP43 Toxicity"

- Are there alteration to the composition of the NPC itself
- Nuclear pore complex coordinates fundamental cellular process
- Nucleoporin mutation can be initiator of cell type specific disease
- Age dependent loss of 8 nucleoporin in iPSN nuclei
- ESCRT-III pathway
- Early optimization of CHMP7 may be an early therapeutic for ALS/FTD

Michael Ward (National Institutes of Health, United States)

"Loss of TDP-43 Function in Neurodegenerative Diseases: From Mechanisms to Biomarkers"

- TDP-43 loss of function alters RNA splicing
- Can cryptic exon de novo synthesis of peptide
- Informatic pipeline to generate a cryptic exon catalog
- RNA and protein degradation: challenging in biomarker development
- Proteomic strategy for mis-splicing biomarkers
- Cryptic peptide detection in TDP-43 KO iPSC neurons
- **Can cryptic peptide have detected in CSF**? **Cryptic peptides are**

expressed in ALS/FTD!

- **iNDI (iPSC neurodegenerative disease initiative) website launch Aug. 8,2022**

Steven Boeynaems (Stanford University, United States)

"Polycation Poisoning is a Pervasive Killing Strategy of Bioactive Peptides in Biology and Human Disease"

- Cationic repeat
- RNA tunes condensate protein composition
- Cationic peptides perturb MT-based transport
- AMP induce coacervation ex vivo
- Other class of bioactive peptides
- supercharged GFP shows differential toxicity
- Target promiscuity is a feature, not in the bug
-

Dongik Park (Aarhus University, Denmark)

"Roles of Sortilin in Frontotemporal Dementia: Identification of Affected Hippocampal Pathways Using Integrated Omics Analysis"

- Sortilin deficiency: decrease in spatial memory, recognitive memory, fear memory extinction
- Significancy: energy metabolism,

Mercedes Prudencio (Mayo Clinic, Department of Neuroscience, United States)

"The Role of TDP-43 and Other hnRNPs in Repressing Cryptic Exon Inclusion in UNC13A"

- Dimerization of TDP-43 is required fir binding and regulating UNC13A splicing

Valina Dawson (Johns Hopkins University School of Medicine, United States)

"Decoding Alpha Synuclein Neurodegeneration"

- PAR (MIF) (AIF)
- PAANIB-1 protects against a-syn PFF-induced pathology in vivo
- PAANIB-1 does not alter the expression of a-syn and MPTP
- GLP-1 receptor agonists protect against pathology of PFF a-syn induced
- cGAS/STING: STING KO is neuroprotective in the a-syn PFF model
- STING is up regulated in human PD
- Winston Churchill

Towfique Raj (Icahn School of Medicine at Mount Sinai, United States)

"The Role of Myeloid Cells in Parkinson's Disease"

- Post-GWAS knowledge gap
- Functional variant and genes remain unknown gene and loci

Dario Alessi (MRC Protein Phosphorylation and Ubiquitylation Unit, United Kingdom)

"Deciphering the LRRK2 Signaling Pathway in Parkinson's Disease"

- Rab protein are key physiological substrate of LRRK2
- Rabs are phosphorylated at very low stoichiometry and pathogenic mutation enhances Rab protein phosphorylation
- What is upstream of LRRK2?
- What is downstream of LRRK2 phosphorylated of Rabs
- LRRK2 phosphorylated Rabs interact with RH2 motif containing effectors
- TMEM55B binds to pRAB: RILPL1 complex
- PPM1H was an siRNA screen as a potential pRab dephosphorylates

Tara Spires-Jones (The University of Edinburgh, United Kingdom)

"Through the Looking Glass: Imaging Synapse Pathology in Alzheimer's Disease"

- Synaptic tsu in human synapse observed with array tomography
- Synaptic oligomeric tau in AD-a potential culprit in the spread of tau pathology through the brain
- Human astrocyte and microglia show
- Oligomeric tau is most prevalent in human synapse
- Oligomeric tau in globular structures immunoEM
- Oligomeric tau is present in synaptic pairs in human brain indicating the potential for trans-synaptic spread
- Astrocytes contain colocalized tau and synapse, more in AD
- Potential mediator of AD synapse phagocytosis-MFG-E8
- MFG-E8 tags AD synapse for engulfment by astrocytes

Christian Haass (Ludwig Maximilians University of Munich, Germany)

"Targeting Microglia Function in Neurodegenerative Diseases"

- 4D9 binds close to cleavage site
- Is TREM2 protective in humans and when do we have to treat?
- Human antagonistic TREM2 antibodies rescue elevatedTREM2 levels and reduce pp-SYk in macrophage isolated from GRN-FTLD
- Microglia activation is reversible
- Abi3(S209F) fails to be phosphorylated and causes microlia morphological changes
- Haass is also part of DIAN!

Mathew Blurton-Jones (The University of California, Irvine, United States)

"Using iPSC-Microglia to Deliver Therapeutic Proteins to the Brain"

- Many AD reisk genes are highly expressed in microglia but not or poor in mouse homologous
- Can maturation of iPSC microglia progenitor withing the mouse forebrain

- Could iPS-microglia transplation also be developed for the therapeutic applications?
- Human microglia delivery of Neprilysin reduce AB level
- CD9 promoter can drive production of Neprilysin

Beth Stevens (Boston Children's Hospital and Harvard Medical School, United States)

"Mapping and Modeling Microglia States to Function in Alzheimer Disease"

- When?
- How do microglia contribute to disease pathogenesis?
- Identification of disease associated of. Microglia (DAM)
- Identifying molecular correlates of amyloid and tau pathology in biopsies od prefrontal cortex
- Goal: a unifying framework for characterization tissue changes in AD
- AD-enriched: lipoprotein particle responsive gene
- How do genetic and environmental challenges alter cell states and functions?
- How dynamic are microglia states? Reversible?
- iMGL states recapitulate human microglia states (GPNMB)
- TREM2 KO iMGLs have impaired phagocytosis and DAM production
- Cell vilages (dropulation and census-seq to understand the impact of polygeneic risk score on microglia AT SCALE)
- How does genetic background affect proliferation?
  - Phenotype score
  - QTL

Avi Samelson (University of California, San Francisco, United States)

"Determinants of Tau Aggregation in Human Neurons"

- Goal: Systemically probe factors that control the conformation endogenous tau in human
- Rotenone increases tau oligomer and total tau levels
- Rnf7 can directly ubiquitinate tau
- Proteasome+ROS
- Decrease in tau oligomers (e.g., MAPT)

Hannah Walgrave (VIB-KULeuven Center for Brain & Disease Research, Belgium)

"Multi-omics Targetome Profiling of MicroRNA-132 for Therapeutic Targeting in AD"

- Combination therapy (miRNA therapy)
- miR-132 is downregulated in AD
- miR-132 is expressed in four main brain cell types
- Integrative genome wide identification of miR-132 targetome
- How to design miRNA KO KD experiment?
  - Using antagomir from QIAGEN (LNA-containing, cholesterol-conjugated oligonucleotides)
- OL adapt a less reactive phenotype upon miR-132 supplementation!
- miR-132 shifts human iPSC-derived microglia to a more homeostatic state
- From De strooper lab/ Salta lab

Michael Strickland (Washington University in Saint Louis, United States)

"Structure of Human Lipidated Apolipoprotein E"

- Lipidation is critical for ApoE function
- Using Monoclonal Fab fragments to catch APOE
- ApoE disulfide-liked homodimer cannot bind DLR

Jungsu Kim (Indiana University School of Medicine, United States)

"The Role of ABI3 in the Pathogenesis of Alzheimer's Disease"

- The function of ABI3 involved cell motility by regulating actin cytoskeleton
- To determine the role of *Abi3* in amyloid-related pathology
- Deletion of *Abi3* decreased clustering of microglia around plaques

in5XFAD mice

Magdalini Polymenidou (University of Zurich, Switzerland)

"Towards Developing Biomarkers for FTLD Subtypes"

- Oligomerization is required for physiological liquid-liquid phase separation of TDP-43
- Mechanism of aggregation of monomeric versus RNA-binding TDP-43?
- PTM in RTD or RRM may triggers theses distinct aggregates
- Induced TDP-43 pathology in minority of neurons
- NPTX2 is a human-specific RNA target of TDP-43
- Why/how is NPTX2 accumulation toxic to neurons?
- Using the system to dissect LOF and GOF

Nicholas Seyfried (Emory University School of Medicine, United States)

"Network-Driven Proteomics to Resolve Brain-Based Biomarkers in Alzheimer's Disease"

- Integrated analysis of the human brain and CSF proteome in AD
- Netwrok-baesed proteomic resolves diverse biology of AD and PD brain (protein-coexpression network analysis)
- Can brain-based biomarker classify asymptomatic in AD
- Glycolysis is a major pathway altered in CDF AD proteomic studies

Donna Wilcock (University of Kentucky, United States)

"Discovery and Validation of Fluid Biomarkers for Vascular Cognitive Impairment and Dementia"

- VCID reflects varied vascular pathologies, and therefore mechanism
- CSF PlGF as a biomarker for cerebral small vessel disease
- Astrocyte and endothelial cell appear to contribute to circulating

Tania Gendron (Mayo Clinic, United States)

"Comprehensive Cross-Sectional and Longitudinal Analyses of Plasma Neurofilament Light across FTD Spectrum Disorders"

- Could plasma NfL facilitates and earlier FTD diagnosis for questionable cases?
- Does NfL associate with disease severity
- Association of plasma NfL with age, gender, and symptom duration
- NfL's prognostic utility could improve patient care, clinical trial efficiency, and treatment outcome estimations
- New lines of investigation can be explored using cross-sectional and longitudinal NfL, demographic genetic clinical, neuropsychological data.

Nimansha Jain (Washington University in St Louis School of Medicine, United States)

"Chronic TREM2 Activation Exacerbates Aß-associated Tau Seeding and Spreading"

- How does targeting TREM2 with an agonist antibody affect tau seeding and spreading in an amyloid model seed with Ad-tau?
- Chronic TREM2 agonist antibody administration increase disease-associated microglia around plaques
- Chronic TREM2 agonist administration doesn't affect AB plaque burden
- Chronic TREM2 agonist administration increases NP-tau pathology, plaque-associated neurotic dystrophy, and loss of peri-plaque synaptic puncta

Louis Dwomoh (University of Glasgow, United Kingdom)

"Activation of M1-muscarinic Acetylcholine Receptor Reduces Pathology and Slows Progression of Neurodegenerative Disease"

- Cholinergic hypothesis: altered acetylcholine expressions
- Research hypothesis:
  Selectively targeting the M1-muscarinic receptor

- Proteomics analysis of prion hippocampus:

Kiara Freitag (German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany)

"Targeting Autophagy to Alter Alzheimer´s Disease Pathology"

- Autophagy inducer(spermidine), spermidine level is dependent on the age!
- 30-day water, and 120d for spermidine
- The spermidine of mechanism: transcriptome of spermidine-treated APPPS1 mice: increase cell motility, proliferation
- Upregulate cell migration
- Proteome of spermidine-treated APPPS1 mice: increase endocytosis, cytokines, autophagy
- Measure cytokine level in APPPS1 mice (increase!)

Haiyan Peng (Alnylam Pharmaceuticals, United States)

"Expanding the Reach of RNAi Therapeutics with Next Generation Lipophilic siRNA Conjugates"

- siRNA design-linker-ligand
- Optimize of RNA chemistry for stability and potency (2'-F, 2'-OME, PS, VP)
- Optimization of lipid conjugate for delivery: C16
- PD/PK model can describe exposure-pharmacology relationship for single and repeat dose in rats
- First siRNA

Certificate of Participation

August 23rd 2022

Hsiang-Hsuan Lin-Wang
graduate student
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Taipei Taipei
Taiwan

This letter certifies your participation as a(n) Attendee at the Gordon Research Seminar on Neurobiology of Brain Disorders held 08/06/2022 - 08/07/2022 at Rey Don Jaime Grand Hotel in Castelldefels, Barcelona [Barcelona], Spain.

Poster Entitled: Identification of pathophysiologically relevant pathways potentially targeted by one type of atypical Parkinsonian patient-associated plasma microRNAs

Dr. Nancy Ryan Gray
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