出國報告（參加國際會議）

主題：第十四屆神經肌肉疾病國際會議 2016

服務機關：臺北榮民總醫院神經內科部周邊神經科
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摘要（含關鍵字）

第十四屆神經肌肉疾病國際會議於 2016/07/05 到 2016/07/09 在加拿大多倫多市召開，職受邀前往發表壁報論文: MAG/SGGL 抗體神經病變中 IgM/SGGL 抗体濃度與病理形態學及電氣學參數的相關性。 本次大會有四個全體會議(plenary sessions)(1, Genetics, 2, Hot Topics, 3, Muscular Dystrophy, 4, Motor Neuron Disease)，八個專題演講(workshop sessions)(1,Metobolic Myopathy, 2, Outcomes in Hereditary Neuropathy, 3, Small Fiber Neuropathy, 4, Controversies Over Large Nerve Biopsy, 5, Interesting Neuromuscular Cases, 6, Ultrasound of Muscle and Nerve，7, Autoantibodies in Neuromuscular Disease, 8, Metabolic Neuropathies) 及八個壁報論文討論會(poster sessions)，本院有五位同仁前往發表壁報論文得到同好專家的互動好評。

會議的主題在探討遺傳肌肉神經病變的病因與治療，而好的治療需要有好的診斷，分子生物學的診療工具進入到核醣核酸序列與大數據結合的時代。另外去氧核醣核酸的編輯技術也帶來嶄新的治療紀元

關鍵字: Neuromuscular diseases, genetics, motor neuron disease, muscular dystrophy, Charcot-Marie-Tooth disease, RNA sequency

一、 目的

神經肌肉疾病國際會議主要是提供國際間從事神經肌肉疾病的臨床醫師及基礎研究人員一個平台，可以互相學習交流，相互砥礪，希望可以給予神經肌病的病患提供更完善的醫療照顧。

神經肌病的研究發展,隨著分子生物學科技的進步及免疫療法的創新,近年來對此類疾病有更深入的了解,以往參加此四年一度的盛會(現今改為兩年一度)。 今年職受邀參加第十四屆神經肌肉疾病國際會議於 2016/07/05 到 2016/07/09 在加拿大多倫多市召開的會議，本次大會有四個全體會議(1, Genetics, 2, Hot Topics, 3, Muscular Dystrophy, 4, Motor Neuron Disease)，八個專題演講(1,Metobolic Myopathy, 2, Outcomes in Hereditary Neuropathy, 3, Small Fiber Neuropathy, 4, Controversies Over Large Nerve Biopsy, 5, Interesting Neuromuscular Cases, 6, Ultrasound of Muscle and Nerve，7, Autoantibodies in Neuromuscular Disease, 8, Metabolic Neuropathies) 及八個壁報論文討論會。於會中，發表我們自己的研究成果,與他人分享,期望早日能找到此類疾病的診療方法及吸收最新的神經肌病相關知識。

二、 過程

2016/7/5 是需付費的教育課程。

2016/7/6 全體會議(Plenary Sessions) 主題為基因學

第一位演講者 Daniel MacArthur，題目是 Genomic Approaches to Diagnosis of Rare Muscle Disease 。

第二位演講者 Stephan Zuchner 題目是 Gene Discovery in Charcot-Marie-Tooth Neuropathies。

第三位講者 James Dowling 題目 RNA Sequence and RNA Analysis

下午的專題演講(Workshop Sessions) Treatment of Myasthenia Gravis

第一位演講者 Gil Wolfe 講題是 Treatment of Myasthenia Gravis

第二位演講者 Susan Iannaccone 講題是 Treatment of MG in the Paediatric Population

另外一場專題演講 Outcomes in Hereditary Neuropathy

第一位演講者 Mary Reilly 講題是 Outcomes in CMT

第二位演講者是 Michael Shy 講題是 Monitoring Hereditary Neuropathies in Clinical Trials

壁報論文(Poster Sessions)

PS1Group4 - 015

CORRELATION BETWEEN IGM PARAPROTEINEMIA AND MORPHOMETRIC PARAMETERS OF SURAL NERVE IN ANTI-MAG, SGGL NEUROPATHY

Kon Ping Lin, Hua Chuan Chao, Cheng Ta Chou, Yi-Chung Lee; Taipei, TW

PS1Group4 - 025

COEXISTENCE OF CHARCOT MARIE TOOTH DISEASE TYPE 1A AND DIABETES: A CLINICOPATHOLOGICAL STUDY

Kon Ping Lin, Hua Chuan Chao; Taipei, TW

PS1Group4 - 026

IN VIVO FUNCTIONAL ANALYSIS OF THE NOVEL BSCL2 P.R96H MUTATION RESULTING IN HEREDITARY MOTOR NEUROPATHY

Cheng-Tsung Hsiao, Pei-Chien Tsai, Yi-Chu Liao, Kon Ping Lin, Yi-Chung Lee; Taipei, TW

PS1Group4 - 027

TWO NOVEL DE NOVO GARS MUTATIONS CAUSE EARLY-ONSET AXONAL CHARCOT-MARIE-TOOTH DISEASE

Yi-Chu Liao, Yo-Tsen Liu, Pei-Chien Tsai, Bing-Wen Soong, Yi-Chung Lee; Taipei, TW

PS1Group4 - 028

BIOPHYSICAL CHARACTERISTICS AND CLINICAL CORRELATION OF GJB1 MUTATIONS IN CHARCOT-MARIE-TOOTH DISEASE TYPE X1

Pei-Chien Tsai, Yi-Chu Liao, Kon Ping Lin, Yo-Tsen Liu, Yi-Chung Lee; Taipei, Tw

2016/7/7 全體會議 講題是 Hot Topics

第一位演講者 Eva Feldman 講題是 Stem Cell Therapy in ALS
第二位演講者Gil Wolfe 講題是RESULTS OF THE THYMECTOMY TRIAL IN MYASTHENIA GRAVIS
第三位演講者James Howard, Jr.講題是REGAIN: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTI-CENTER PHASE 3 STUDY OF THE SAFETY AND EFFICACY OF ECULIZUMAB IN SUBJECTS WITH REFRACTORY GENERALIZED MYASTHENIA GRAVIS
第 四 位演講者Richard Barohn 講題是APPROACH TO PATIENTCENTERED OUTCOMES RESEARCH
第五位演講者Carsten Bonnemann講題是DO WE STILL NEED MUSCLE BIOPSY IN THE ERA OF ULTRASOUND?
第六位演講者Mazen Dimachkie 講題是THERAPEUTIC APPROACHES TO INCLUSION BODY MYOSITIS
第七位演講者David Adams 講題是TREATMENT OF AMYLOID NEUROPATHY

下午第一場專題演講 講題是 Small Fibre Neuropathy
第一位演講者David Adams講題是AMYLOID NEUROPATHY AS A MODEL OF SMALL FIBER NEUROPATHY
第二位演講者Giuseppe Lauria, 講題是DIAGNOSIS OF SMALL FIBRE NEUROPATHY
另外一場專題演講 講題是Controversies Over Large Nerve Biopsy
第一位演講者Anthony A. Amato講題是NERVE BIOPSY ARE RARELY NEEDED
第二位演講者P James Dyck, 講題是IT IS VALUABLE

2016/7/8 全體演講 講題是 Muscular Dystrophy
第一位演講者Dongsheng Duan,講題是GENE THERAPY FOR MUSCULAR DYSTROPHY
第二位演講者Dana Martin 講題是RNA THERAPEUTICS FOR DUCHENNE MUSCULAR DYSTROPHY
第三位演講者Charles Thornton,講題是ANTISENSE THERAPY FOR MYOTONIC DYSTROPHY
第 四 位演講者Ronald Cohn 講題是CRISPR BASED GENE EDITING FOR MUSCULAR DYSTROPHY

下午第一場專題演講 講題是 Interesting Neuromuscular Cases
總共有 6 個有趣的神經肌病個案呈現給聽眾，相當有趣少見的個案
另外一場專題演講 講題是Ultrasound of Muscle and Nerve
第一位演講者Steven Shook,講題是NEUROMUSCULAR PHYSICIANS SHOULD PERFORM NM ULTRASOUND
第二位演講者Linda Probyn, 講題是RADIOLOGISTS SHOULD PERFORM NM ULTRASOUND

三、 心得

會議的主軸在探討遺傳肌肉神經病變的病因與治療，而好的治療需要有好的診斷，分子生物學的診療工具進入到核醣核酸序列與大數據結合的時代。另外去氧核醣核酸的編輯技術也帶來嶄新的治療紀元。

由於會議內容豐富多樣， 職主要的心得有以下四個研究 略述摘要如下

GENOMIC APPROACHES TO DIAGNOSIS OF RARE MUSCLE DISEASE (Daniel MacArthur *Medical And Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA, US*) --Genomic technologies have profoundly changed our ability to uncover the genes underlying a wide range of rare Mendelian diseases. Here I describe three major technological advances in genomic approaches to rare disease diagnosis, and their application to neuromuscular disease. Firstly, I discuss the development of a massive reference panel of "healthy" exomes, the Exome Aggregation Consortium (ExAC) and demonstrate how ExAC data can be used to more effectively filter the variants identified in rare disease patients. Secondly, I outline the value of whole-genome sequencing in the discovery of causal variants missed through exome sequencing. Finally, I describe a pilot study on the application of muscle transcriptome sequencing (RNA-seq) on a set of over 40 exome-unsolved muscle disease cases, and the high resulting diagnostic yield from discovery of splice-disrupting and expression-altering variants. Finally, I outline several unresolved challenges of genomic diagnosis in rare disease cases.

RNA SEQUENCE AND RNA ANALYSIS (James J. Dowling *Neurology, Hospital for Sick Children, Toronto, ON, CA)*-- The application of next generation sequencing has ushered in a revolution in mutation discovery and clinical genetic diagnostics. However, despite its now widespread use in patients, the cause of disease remains unsolved in nearly 50% of cases of genetic neuromuscular disease. This lack of knowledge creates significant barriers to diagnostics, clinical care, and therapy development. One potential explanation for this knowledge gap is that many mutations reside in the non-coding genome. Such mutations are not assessed by current testing modalities such as gene panels and whole exome sequencing. We believe that RNA analysis (via RNA sequencing or RNAseq) is the ideal modality for overcoming these challenges, for identifying and interpreting non-coding mutations, and thus for bridging the current diagnostic gap. In this study, I will describe our efforts at mutation discovery using RNAseq as a diagnostic modality in childhood muscle disease, and will discuss the broader applicability of RNAseq to all genetic disorders of the peripheral nervous system.

STEM CELL THERAPY IN ALS (Eva L. Feldman et al. *Emory University, Atlanta, GA, US; University of Michigan, Ann Arbor, MI, US; Massachusetts General Hospital, Boston, MA, US; Neurology, MGH, Boston, MA, US; Neuralstem, Inc., Germantown, MD, US; Department of*

Neurology, University of Michigan, Ann Arbor, MI, US) -- Cellular therapies offer multiple benefits to combat the complex pathogenesis of amyotrophic lateral sclerosis (ALS), a fatal disease characterized by progressive motor neuron degeneration. While several cell types and delivery strategies have been examined, our experience developing an intraspinal transplantation strategy employing human spinal stem cells (HSSCs) has led to two first-in-human FDA-approved clinical trials. The Phase 1 trial followed a risk-escalation design whereby 15 ALS patients were subjected to increased risk across 5 cohorts based on their level of disability at the time of surgery and the number and placement of injections. Final doses ranged from 500,000 to 1 million cells and were delivered in 5 unilateral or 10 bilateral injections targeting the lumbar and/or cervical spinal cord. Results demonstrated that the intraspinal stem cell transplantation strategy was safe, feasible, and well-tolerated, and monitoring of clinical progression further revealed preliminary insight into potential windows of stem cell biological activity. In the subsequent Phase 2a trial, the safety of increasing stem cell doses ranging from 2 to 16 million cells, which were achieved via increased concentrations per injection and numbers of injections, was assessed. Analyses of the results are ongoing and will be presented; however, the approach was well-tolerated across all cohorts, including the final cohort which received 8 million cells over 20 injections in both the cervical and lumbar spinal cord regions. Comparison of patient functional outcome measures following the procedure with historical control groups also revealed that the therapy did not accelerate disease progression, further verifying safety, and potential windows of biological activity were again observed. Moreover, insight into potential outcome measures that correlate with ALSFRS-R scores were examined to inform future trial phase endpoints, and the Phase 2a trial was expanded to include 3 surgical centers, supporting the feasibility of future larger-scale trials. Overall, our progress to date supports continued examination of this therapeutic strategy, and future trial phases assessing efficacy are being planned.

CRISPR BASED GENE EDITING FOR MUSCULAR DYSTROPHY(Ronald D. Cohn Clinical & Metabolic Genetics, The Hospital for Sick Children, Toronto, ON, CA)--Clustered regularly interspaced short palindromic repeat (CRISPR) has arisen as a frontrunner for efficient genome engineering. However, the potentially broad therapeutic implications are largely unexplored. Here, to investigate the therapeutic potential of CRISPR/Cas9 in a diverse set of genetic disorders, we establish a pipeline that uses readily obtainable cells from affected individuals. We show that an adapted version of CRISPR/Cas9 increases the amount of utrophin, a known disease modifier in Duchenne muscular dystrophy (DMD). Furthermore, we demonstrate preferential elimination of the dominant-negative FGFR3 c.1138G>A allele in fibroblasts of an individual affected by achondroplasia. Using a previously undescribed approach involving single guide RNA, we successfully removed large genome rearrangement in primary cells of an individual with an X chromosome duplication including MECP2. Moreover, removal of a duplication of DMD exons 18 – 30 in myotubes of an individual affected by DMD

produced full-length dystrophin. Our findings establish the far-reaching therapeutic utility of CRISPR/Cas9, which can be tailored to target numerous inherited disorders.

四、 建議事項

1, 成立基因醫學部統籌分子生物學相關的資源人力及研究發展

2, 鼓勵年輕醫師參加國際會議

附錄(如附件)