➢ Introduction

It is my honour to represent Families of Spinal Muscular Atrophy Charitable Trust (FSMA (HK)) to attend the 15th Annual International Spinal Muscular Atrophy Research Group Meeting, 2011. This year, the meeting was held from 23rd to 25th of June, in Walt Disney World Swan Resort, Orlando, Florida of the United States. There were over 200 delegates from 70 institutions over 11 countries attending the conference. Most of the attendees were scientists while around 20 medical doctors were there. Drug companies had representatives in this meeting as well.

The meeting started with a special session "Comparative SMA Pathology in Mice and Man with Therapeutic Implications". Other sessions included "Clinical Research Session", "SMA Models and Observed Phenotypes", "SMN Molecular Functions and SMN Regulation" and "Therapy Development Session". Two poster sessions covering seventy seven posters of different topics were also included. There were social functions that enabled the researchers to meet the SMA patients and families.

The three-day program covered a variety of SMA-related topics, from basic science, animal models, clinical researches to new therapeutic options. I shall briefly summarize the basic science findings and the new animal models in my report. The clinical researches and the novel therapeutic modalities will be covered in more details.

➢ Basic Science and Animal Models

There were presentations on the molecular aspect of SMN protein, topics included:

- The cellular functions and pathways interacting with the SMN proteins. The roles of HuD, Plastin-3 (PLS3), E3 Ubiquitin ligase in association with SMN protein had been discussed.
- The role of SMN protein in pancreatic development.
- The structure of SMN protein.

Topics related to the anatomical and physiological changes in SMA patients included:

- The roles of motor neuron, interneuron, neuromuscular junction and muscle in the pathogenesis of SMA.
- The anatomy of neuromuscular junction, microvasculature and the pathological changes in SMA patients.

Of note, the cholinergic interneuron had been the first time being considered to have a pathogenic role in SMA. Recent studies on SMA animal models suggested motoneuron death was a relatively late event which was preceded by functional defects of the presynaptic part of the neuromuscular synapse and by loss of synaptic input on

motoneurons from spinal interneurons. Based on this concept, a pilot study using 3,4 diaminopyridine (DP) on type III patient was initiated by Dr. Swoboda's group. DP was potassium channel inhibitors increasing the release of acetylcholine at central and peripheral synapses, which could theoretically modified the biochemical profile of interneurons.

In terms of animal models, a new SMA pig model was created by Dr. Lorson's group (University of Missouri). Piglets with SMA can now be used for studies in addition to mice.

➢ Clinical Researches

There was a half-day session for clinical researches. Topics included:

- Congential heart disease and SMA.
- Electrical impedance myography as a biomarker for SMA.
- Home monitoring of pulmonary function in SMA type II patients.

There were also presentations on the efficacy of valporic acid and salbutamol on SMA patients. The findings of some of these studies had been released before the meeting. Using valporic acid, the VALIANT trial failed to show any benefit on ambulatory SMA adults. A previous CARNIVAL trial by Dr. Swoboda et al, using valporic acid on non-ambulatory SMA paediatric subjects demonstrated similar negative results. The result of a phase 2 randomized double-blind study using salbutamol on SMA type III patients by an Italian group was still in the analytical stage.

Olesoxime (TRO 19622), a neuroprotective compound, is at phase II clinical trial in European countries. Preliminary studies showed olesoxime was well tolerated and revealed no major side effect. The efficacy of other drugs, such as hydroxyurea and phenylbutyrate had not been discussed in the meeting.

➢ New Therapeutic Modalities

Stem cell, antisense oligonucleotide (ASO) and gene therapy treatment were discussed in the therapy development session.

Stem Cell Therapy

Two groups, Corti et al (University of Milan, Italy) and Keirstead's group (California Stem Cell Inc., US) presented their works on stem cell treatment. Both groups demonstrated functional benefits in mouse models. Keirstead's group had already filed an investigation new drug (IND) application in November 2010. There were no major new findings after the IND. Stem cell treatment trial for SMA is now on clinical hold.

Antisense Oligonucleotide (ASO)

For ASO therapy, Dr. Krainer's group (Cold Spring Harbour Laboratory, New York, US) and ISIS Pharmaceuticals representatives talked about the potential drug candidate ISIS 396443. This drug candidate is a MOE-type ASO against ISS-N1 of exon 7 SMN2 gene. Intrathecal bolus injection in SMA-mouse model had good effect. Experiment using non-human primate (cynomolgus monkey) showed good CNS distribution and drug concentration. The ISIS 396443 is now currently evaluated in preclinical toxicology studies. The ASO phase I clinical trial on SMA type I patient will probably commence in Q4 of 2011 or Q1 of 2012. A poster presentation by Dr. Burges' group (Ohio State University, Ohio, US) showed correction of SMA mice using morpholino type ASO (another type of ASO) after intrathecal injection. The two different groups indicated that ASOs were promising candidate for SMA treatment and the results were reproducible.

Gene Therapy

Following the work of SMN1 transfection study using AAV9 by Dr. Kasper's group (Nationwide Childern's Hospital, Ohio, US), further experiment using AAV9-GFP on non-human primates (cynomolgus monkey) demonstrated system wide transgenic expression after *intravenous* injection. Similar positive results had been obtained using pig models (Ohio State University).Dr. Barkats's group (Universite Pierre et Marie Curie, Paris, France) showed similar good transduction result after *intramuscular* injection of AAV9-GFP in mice. Preliminary toxicology studies using mice and monkeys revealed a satisfactory safety profile. Dr. Kasper's group had the first pre-investigation new drug (pre-IND) meeting with FDA in February in 2011. Further toxicology analysis is underway and formal IND will probably be done in late 2011 or next year.

New "Oral" Drugs

PTK therapeutics Inc. (New Jersey, US) presented a set of brand new orally bio-available brain penetrable small molecules with good effects on SMA-mice. The nature and structure of these small molecules were not released in this meeting. The drugs PTC-SSN and PTC-SSQ given *intrathecally* once followed by *oral* maintenance doses rescued the SMA-mice. These promising compounds are undergoing further evaluation.

➢ Summary and Suggestions

The meeting presented some of the recent advances in different research fields of SMA, from basic science to novel therapeutic options. Some of the most promising treatment modalities such as the antisense oligonucleotide (ASO) by ISIS pharmaceuticals and SMN1 gene therapy using AAV9 by Dr. Kasper's group are approaching the translational stage of development. The ASO therapy will be on clinical trial in late 2011 or early next year.

If there is a narrow therapeutic window for SMA patients, I think Hong Kong doctors and

FSMA (HK) should be more alert on these new clinical trials and seek chances to collaborate with centers overseas. Patients can then be treated promptly and Hong Kong will not lag behind in terms of new treatments for SMA.

In addition, the Taiwanese appear quite active and renowned for SMA researches. There were well written articles in peer reviewed journals, abstracts and poster presentations in the current meeting by them. Forming a clinical/patient self-help group network with them may facilitate multicentre trial, including the potential new novel therapy trials in the future.

Finally, I would like to thank Mrs. Fok (President of FSMA,HK), Prof. Virginia Wong (Department of Paediatrics, HKU), Dr. Danny Fok (Honorary Medical Consultant, FSMA, HK), the Executive Committee Members of FSMA (HK), Mrs. Yim, Carmen Yau and all other staff of the FSMA (HK) for their efforts spending on SMA patients throughout the years.

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