Summary report of the 11th Annual Conference of International Association of Neurorestoratology (IANR)

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The 11th Annual Conference of the International Association of Neurorestoratology (IANR) was held from October 2nd to 4th at the University of Rutgers, New Jersey, USA, in which the most highlight was to report many frontier clinical trials. This summary report tries to display mainly presenting achievements in this conference.

The contents are brilliant, which cover clinical trials of spinal cord injury (SCI), brain injury, Parkinson’s disease (PD), stroke, Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS) and Huntington’s disease (HD). Therapeutic achievements by neurorestorative techniques or strategies including neuromodulation, brain stimulation, neural feedback, brain-computer interface (BCI), novel cells, nanomedicine, peripheral nerve repair, revascularization technology and new materials for bioengineering, etc. have been reported. The Raisman Young Scholars Awards were organized to contest and reward to the winners.

The second meeting of the Fourth Council Board of the IANR discussed and decided that the 12th Annual Conference would be held in Jordan and the 13th Annual Conference would be held in Poland. The Council Board also fully discussed how to make the association's official journal Journal of Neurorestoratology better and more popular.

The highlight of the conference was to actively promote multi-country and international cooperation to conduct multi-center randomized controlled clinical trials. As we know, cell transplantation of multi-country single-center was tested in different diseases or damage, especially for complete SCI in latest 20 years. Involving cells include olfactory ensheathing cells (OECs), cord blood mononuclear cells, mesenchymal stromal cells (MSCs) and Schwann cells (SCs), etc.
Integrated neurorestoration (including cell therapy, neuromodulation and rehabilitation etc.) treatment has been able to restore patients with complete chronic SCI some neurological functions; and partial patients can even stand and walk again. However, in the medical field, many doctors still maintain the view that there is no neurorestorative effective treatment for chronic SCI. So, the theme of this annual meeting is “Neurorestoratology requires high-level evidence-based medicine”.

Below, this summary report shows parts of impressive presentations of this conference to readers.

1 Clinical trials

1.1 Clinical trials for SCI

Wise Young from USA reported that Stemcyte has proposed a Phase IIb clinical trial to assess the safety, feasibility and efficacy of transplanting HLA-matched umbilical cord blood mononuclear cells (UCBMNC) into the spinal cord for 27 chronic complete SCI people, with and without lithium carbonate followed by 6 months of intensive locomotor training. Code-named US102D will randomize 27 patients to three treatments groups: transplantation of a total of 6.4 million HLA-matched UCBMNC into spinal cord and a 6-week course of oral placebo, transplantation of the cells and a 6-week course of oral lithium carbonate. All the patients will receive 6 months of intensive locomotor training. On January 13th of 2017, Stemcyte submitted an initial new drug / device (IND) application to the Food and Drug Administration (FDA) for permission to carry out this trial. The FDA requested additional animal studies to assess the toxicity and migration of UCBMNC transplanted into them spinal cord. After a year of extensive animal studies, Stemcyte showed that UCBMNC were well tolerated when transplanted into immune-deficient rats, exhibited little or no toxicity when transplanted into the spinal cord, did not result in any tumors or loss of function in the animals. The IND was resubmitted to the FDA and has essentially been approved except for a clinical hold of the trial until final validation of the hospital facility that will be preparing the cells for transplantation. The trial will be initiated soon.

Poon Wai Sang from Hong Kong of China summarized the work of China Spinal Cord Injury Network. More than 600 patients with chronic spinal cord injuries into 8 clinical studies were recruited over a 5-year period, gathering information on clinical outcome natural history and efficacy information for patients treated with lithium, methylprednesolone and human umbilical cord blood mononuclear cells. A 6-month course of intensive anti-gravity walking exercise has been demonstrated to convey benefits to sphincter function.

Hongyun Huang from China reported the design that was to explore the safety and neurorestorative effects of intramedullary decompression surgery for acute complete spinal cord contusion injury.

Kyoung-Suok Cho from South Korea collected data from 143 patients with cervical SCI. Based on the time to surgical decompression, they grouped patients into an ultra-early group (decompression within 8 hours of presentation) with 8 cases, an early group (within 8–72 hours) with 75 cases, and a late group (> 72 hours) with 60 cases. They compared the improvement in abbreviated injury scale (AIS) grade from admission to discharge in each patient group. Results showed that the patients who received surgery less than 8 hours after presentation had a significant improvement in AIS grade from admission to discharge, as well as a higher absolute AIS grade at discharge. There was no difference in AIS grade for patients who received surgery 8–72 hours after presentation and those who received surgery > 72 hours after presentation. So, surgical decompression within 8 hours in traumatic SCI may optimize neurological recovery, especially in patients with cervical SCI.

Moviglia Brandolino Maria Teresita from Argentina reported intravascular implant with neural progenitor cells and lymphocytes with intensive rehabilitation program for patients with chronic and complete SCI, who showed muscular functional recovery.

Keung Nyun Kim from South Korea reported that open-label and nonrandomized controlled clinical trial of human neural stem/progenitor cells (hNSPCs) transplanted into the injured cord after traumatic cervical SCI and showed modest neurological benefit up to 1 year after transplants.

Lin Chen from China compared and analyzed the effect of olfactory ensheathing cell intramedullary
transplantation in multi-centers for complete chronic SCI. The cell implantation into the spinal cord parenchyma is effective for neurological functional recovery and enough rehabilitation training is necessary for the integration of motor recovery after cell transplantation, but improper procedures may lead to ineffective results.

Hooshang Saberi from Iran performed a prospective, double-blind, placebo-controlled and parallel randomized clinical trial through subcutaneous Granulocyte-Colony stimulating factor (G-CSF) administration for incomplete subacute traumatic SCI. The results showed that G-CSF administration made patients with incomplete subacute traumatic SCI having significant motor, sensory, and functional improvement.

Adeed Al-Zoubi from Jordan reported the results of cell therapy for patients with SCI, who showed some functional restoration.

1.2 Clinical trials for neurodegenerative diseases

Hongyun Huang and Gensheng Mao from China demonstrated the mid-term results of a series cell therapy of multicenter, randomized, double-blind and placebo-controlled cell treatments for stroke, Parkinson’s disease and Alzheimer’s disease, etc. Preliminary results show partial involving trial’s patients getting some benefits without side-effect, which is expected to provide evidences of higher-level evidence-based medicine, and ultimately makes cell therapy to be a routine therapeutic technique for neurological diseases and damage.

Anna Sarnowska reported preclinical and clinical outcome of intraspinal transplantation of autologous adipose-derived regenerative cells (ADRC) in six patients with amyotrophic lateral sclerosis. The intraspinal ADRC transplantation at the Th10/11 level was proved safe and well tolerated. In two patients, the neurosurgery induced reduction of the muscle tone, which resulted in improved walking capacity of a one-month duration, objectively measured in one case. There was also a reduction of progression rate of the walking impairment within 3 months after the transplantation in the same patient. From all applied measures, Motor Unit Number Index (MUNIX) proved to be the first and the most sensitive tool in identifying fine changes at the muscle level. It was markedly more sensitive than amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) and Medical Research Council (MRC) dyspnea scale. Moreover, in longitudinal studies it was reduced not only in paretic but also in presymptomatic muscles. The dynamometry was the closest measurement to MUNIX, both on the upper and lower limbs level. The Modified Ashworth Scale was a sensitive tool in a potential patients’ stratification according to the spasticity level. Among the analyzed in cerebrospinal fluid (CSF) cytokines/chemokines only six factors correlated with the therapeutic effect of ADRC treatment. 24 hours after ADRC injection, the level of all six cytokines was elevated, but after 3 months decrease of proinflammatory (TNFα, IFN-γ and IL-1β) cytokines and increase of the growth factors and anti-inflammatory/regressive agents like IL-6, bFGF and MMP-9 were observed.

Shinn-Zong Lin conducted a phase I pilot trial to study the safety and efficacy of intra-cerebral implantation of autologous adipose-derived stem cells (ADSC) over peri-stroke area. Three patients were included. Clinical evaluations included NIHSS, Fugl-Meyer score and Barthel Index of Activities of Daily Living. These patients showed remarkable amelioration of stroke symptoms after ADSC transplantation and achieved independent activity during their last follow-up (1, 3 and 6 months). There are no serious adverse effects from implanted cells or surgical procedures.

Alok Sharma has shown that cell therapy is a safe and an effective treatment option for some incurable neurological disorders. The evidence of they have published 9 clinical studies demonstrating the safety and efficacy of intrathecal transplantation of autologous bone marrow mononuclear cells in various incurable neurological disorders such as autism spectrum disorder (ASD), cerebral palsy (CP), intellectual disability (ID), muscular dystrophy (MD), ALS, thoracolumbar and cervical SCI, traumatic brain injury (TBI) and brain stroke. In ASD, 92% of 32 cases showed improvement in different aspects of Indian Scale for Assessment of Autism (ISAA) along with improved scores of Clinical Global Impressions Scale (CGI) and Functional Independence Measure (FIM) indicating cognitive and functional improvements. In CP, 95% of 40 patients showed improved oromotor activities, neck control, sitting, standing, walking balance and speech with improved metabolism recorded in the PET CT scan brain. In ID, outcome of 29
patients of the intervention group was compared to that of 29 patients from only rehabilitation group and it was found that all patients in the intervention group showed improvement while, there was no improvement in 20.69% patients from only rehabilitation group. In MD, 86.67% of 150 MD patients showed improved strength in trunk, upper and lower limbs and gait. In ALS, it was found that the survival duration of the treated population \((n = 37)\) was 30.38 months more than that of the control group \((n = 20)\). In SCI, 91% of 110 thoracolumbar SCI patients and 74% of 56 cervical SCI patients showed improvement in spasticity, sensation, trunk control, bladder management, standing and sitting balance, ambulation and activities of daily living (ADLs) along with FIM, American Spinal Cord Injury Association (ASIA), and electromyogram/nerve conduction velocity (EMG/NCV). In TBI, 93% of 14 TBI patients displayed improved balance, voluntary control, muscle tone, oromotor activities, cognition, coordination, speech, ambulation and ADLs after intervention. In 24 patients of brain stroke, better outcome was observed in patients with ischemic stroke as compared to haemorrhagic stroke with improvement in ambulation, hand function, standing and walking balance.

2  Neuromodulation and brain machine interface

Kenneth L. Shepard from USA developed a high-channel-count bioelectronic interface to sensory cortex. The prototype device has 65 k electrodes for subdural stimulation and recording. The entire device, including the electrode array and all the associated electronics, is integrated onto a single integrated circuit chip fabricated in a complementary metal-oxide-semiconductor (CMOS) process. This chip is thinned to less than 20 microns while renders it flexible and conformal to the brain. The chip is inserted with a small craniotomy which allows the chip to be inserted in under the dura and skull. A “relay station” outside the skull communicates and powers the device wirelessly while acting as a standard 802.11 wifi device.

Dennis J. McFarland from USA has shown that over the past 30 years, brain-computer interface research and development has grown into a very active and exciting field. Its primary goal has been to restore communication and control to those with severe neuromuscular disabilities. At the same time, it has become increasingly apparent over the past decade that BCIs might also improve sensorimotor rehabilitation for people with strokes or other disorders, BCIs may be able to complement existing therapies and enhance functional recovery. Several different BCI-based rehabilitation strategies are under study, the initial results are promising. Given the extremely large numbers of people who might benefit, neurorehabilitation may eventually prove to be the most important application of BCI technology.

Yong Hu from Hong Kong of China reported that brain stimulation, neural feedback and brain machine interface with rehabilitative interventions can improve neurological function for various neurological diseases and disorders, such as stroke or brain injury and SCI. The main mechanism is the brain plasticity or neuroplasticity refers to the neural functional and structural changes in response to neuromodulation and training.

Winfried Mayr from Austria introduced that integration of externally controlled afferents and residual motor control of impaired central neural system (CNS) opened new effective possibilities in restoring movement and artificial afferent input to spinal interneuron networks provided important complementary options to influence movement and sensory functions.

3  Neurorestorative pharmacotherapy

Non-invasive techniques based on colloidal carriers could represent a huge potential, since nanocarriers (polymeric nanoparticles, nanoliposomes, solid-lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), micelles, nanogels and dendrimers could protect the drugs (or gene material) and deliver them to CNS. Giovanni Tosi from Italy introduced the main advantages of the use of nanomedicine-based approach for innovation in crossing the most “defensive” barrier, with relevance to neurodegenerative diseases.

4  Tissue engineering and bioengineering

Wuh-Liang Hwu used a gene therapy for aromatic L-amino acid decarboxylase (AADC) deficiency results
in de novo dopamine production and supported durable improvement in major motor milestones. They have treated 25 patients using a single administration of GT-AADC delivered bilaterally to the putamen by stereotactic infusions during a single, operative session in single-arm, open label clinical studies in their hospital. Patients received a total dose of either $1.8 \times 10^{11} \mu g$ total of GT-AADC ($n = 21$) or $2.4 \times 10^{11} \mu g$ total of GT-AADC ($n = 4$). Of the 25 children, 3 are now more than 7-year, 4 are more than 6-year, and 9 are more than 2-year post-gene therapy. Clinical results of the first 18 patients were compared to natural history cohort. At baseline (21 months to 8.5 years old), no child had developed full head control, sitting unassisted or standing capability, consistent with the published natural history cohort of severe AADC patients. After gene therapy, all patients exhibited increase scores in motor scales and gained new motor function. Objective evidence for de novo dopamine production was obtained from CSF homovanillic acid (HVA) levels and $6-[^{18}F]-fluoro-l-DOPA$ (FDOPA) positron emission tomography (PET). CSF HVA levels increased significantly one year after gene therapy. FDOPA uptaken in bilateral putamens also increased one year after gene therapy, and was stable over five years after gene therapy.

Damien P. Kuffler showed that the application of platelet-rich plasma (PRP) to the ends of nerve stumps reduces / eliminates chronic neuropathic pain. Then, they have finished a clinical study in which following extremity amputations, the major exposed nerve stumps were secured within a closed ended collagen tube filled with PRP to prevent the development of phantom limb pain (PLP).

## 5 Neurorestorative surgery

Justin Brown from USA introduced the procedures applied to the central or peripheral nervous system that correct deficits by augmenting neural control, restoring neural connectivity and redistributing intact residual functions.

Hongyan Han from China reported that 528 patients with Moyamoya disease got novel combined bypass surgery, that is, superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and encephaloduro-myo-arterio-pericranio-synangiosis (EDMAPS). Those revascularization procedures restored some neurological functions by improving cerebral hemodynamics in both the MCA and anterior cerebral artery (ACA) territories.

## 6 Therapeutic policy of Neurorestoratology

Russell Andrews from USA presented related issues of Neurorestoratology at the policy level: disaster response centers. To improve morbidity / mortality in disasters both natural and man-made (terrorism, building collapse and transportation accidents), disaster response (DR) must be on-site within 24 hours, not the days to weeks of current DR (e.g., UN, WHO, Red Cross).

Ziad M. Al Zoubi from Jordan pointed out that cellular therapy has some obstacles to the growth and development of this new form of treatment. Based on several documents and researches, it is proposed to recommend to regulatory bodies and medical associations an alternate way of looking at regulations for cell therapy so that simultaneous to ensuring that only safe and effective treatment are offered to patients, greater availability of these new treatment options is also encouraging. These recommendations are greater permissiveness for use of cell therapy in incurable conditions, identifying legitimate cell therapy services, promoting medical innovation, respecting the rights of patients to choose treatments, recognizing the valid compassionate use of unapproved therapies, recognizing the significance of small functional gains, giving importance to practice based evidence and existing published literature and having differing regulations for the different types of cell therapies. At the same time, he suggested to widen the era of researches during the next conference to include the trials on the musculoskeletal organs which is primarily related to Neurorestoratology, during the next conference in Amman / Jordan there will be sessions on the trials of cell therapy in bone, joints and muscles.

Gustavo A. Moviglia proposed the clinical trial of cellular therapy for stroke during its subacute phase. Based on the facts and what they have observed during their pre-clinical and clinical experience working on SCI, he suggested to perform a Proof of Concept Clinical trial, if days 6 and 8, will be optimal for the treatment of stroke patients with endothelial cells-central nervous system (EC-CNS) and neural progenitor
cells (NPC), respectively. It is done with the goal to stabilize, probably improve, the brain lesion and the clinical outcome of these patients.

Shiqing Feng from China analyzed the problems of clinical cell transplantation in the treatment of spinal cord injury and suggested to better understand the merits, demerits and precise function of different cells for SCI.

Sang Ryong Jeon from South Korea proposed that the future strategy should focus on the ways to enhance the effects of cell therapy such as materials to be combined with cells, gene modification for secreting trophic factors or cytokines.

Siwei You from China suggested to make combinatorial efforts of basic and clinical vision scientists for clinical applications of these achievements, then effectively enhanced the restoration of injured optic nerve.

### 7 Basic and preclinical research of Neurorestoratology

Jason B. Carmel from USA targeted the spinal cord through the strong interaction of the corticospinal tract (CST) and large diameter afferent fibers, which mediated the senses of joint position and muscle tension. They hypothesized that repetitive pairing motor cortex and sensory spinal cord would strengthen sensorimotor integration in the cervical spinal cord of rats. Indeed, sub-threshold spinal cord stimulation strongly augments motor cortex evoked muscle responses when they are timed to arrive synchronously in the spinal cord. When pairing is performed repeatedly, there is more than a doubling of muscle responses that lasts for up to 2 hours after just 5 minutes of pairing. They also tested the necessity and sufficiency of the CST and large-diameter afferents by selective viral inactivation. Both CST and large diameter afferents were necessary for the paired stimulation effects; inactivation completely abrogated the paired stimulation effects. Selective stimulation of the CST at the pyramid or dorsal roots was also enough for the paired stimulation effect. Finally, they examined the effects of paired stimulation on motor outcomes after spinal cord injury. Adult rats were subjected to a moderate C4 contusion injury followed ten days later by ten days of paired stimulation. Control rats had sham stimulation and all rats were tested by blinded evaluators on two tests of skilled motor function. Rats with electrical stimulation had improved function on both a skilled walking task and a food manipulation task. Since motor cortex and cervical spinal cord are safely stimulated in people, this approach could be translated quickly to clinical trials.

Fabin Han from China reported that rats with transplanted inducing pluripotent stem cells to neural stem cells (iPSC-NSCs) showed progressive improvements in motor behaviors compared to controls from weeks 4 to 16 post-grafting. These results demonstrated the efficacy and usefulness of the growth cocktail in combination with iPSC-NSCs transplantation in 6-OHDA lesioned rats, which provided a promising cell-based treatment strategy for the PD patients.

Ki Bum Lee from USA focused on the synthesis and utilization of multifunctional nanoparticles as drug and gene delivery vehicles to manipulate the expression of key genes in stem cells and somatic cells for cellular reprogramming. One of the approaches includes developing an artificial, nanoparticle-based transcription factor (termed NanoScript) to provide an innovate approach to differentiate stem cells in an effective, selective and non-viral manner. Another approach includes combinatorial nanoarrays of graphene-nanoparticle hybrid structures using nanoparticles and chemically derived graphene, graphene-nanofiber hybrid scaffolds and biodegradable hybrid nano-scaffolds were developed and utilized to deliver genetic materials into stem cells for controlling their neural-differentiation pathways and neuronal behaviors.

Mari Dezawa from Japan described one endogenous pluripotent multilineage-differentiating stress enduring (Muse) cells, which may revolutionize medical care. Muse cells are naturally existing unique endogenous stem cells that are non-tumorigenic and are pluripotent-like. They express pluripotent markers, can generate cells representative of all three germ layers from a single cell and are able to self-renew. Recently, Muse cells are shown to circulate in peripheral blood in healthy donors, and the number increases in stroke and acute myocardial infarction (AMI) patients in an acute phase, suggesting that endogenous Muse cells are mobilized into peripheral blood to repair tissues while their number is not enough to recover, and that supply of exogenous Muse cells is expected to deliver
statistically meaningful functional recovery. The phase I clinical study for AMI and stroke is conducted based on intravenous drip of donor-derived Muse cells.

Inbo Han from South Korea reported that injecting iron oxide nanoparticle-incorporated exosome-mimetic nanovesicles from mesenchymal stromal cells (NV-IONP) could enhance the blood vessel formation, attenuate the inflammation and apoptosis in the injured spinal cord, and consequently improve the spinal cord functions.

Francesca Citthetti from Canada reported her preliminary data, which confirmed the contribution of the circulatory system to mutant huntingtin (mHtt) dissemination. This means that mHtt can cross the blood-brain-barrier and spread within the brain of wild-typ (WT) mice. Also, this technique will further determine if rejuvenating blood factors from the healthy WT parabiont can alleviate HD-related pathology/phenotype in transgenic animals.

Na Liu from China reported that adipose-derived stromal cells overexpressing CX3CR1 demonstrated an increased migration ability in both in vitro and in vivo models, and improved therapeutic outcomes in the intracerebral hemorrhage animal model.

8 Short summary

Both scientists and physicians in the world are trying their best to explore more effective neurorestorative therapies and push them to translation into clinic. From clinical viewpoints, it is very urgent to do multi-center randomized double-blind controlled clinical trial for promising and potential neurorestorative therapies, in order to make them to be routine therapeutic methods for patients with neurological diseases and damage including chronic complete SCI.

Disclosure

The authors declare no competing interests.

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