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The 445th International Symposium on Therapy

The 445th International Symposium on Therapy was held by the Zoom Webinar on July 16, 2020. Dr. Ryozo Nagai, Director of the International Medical Society of Japan (IMSJ), presided over the meeting.

Advances in gene therapy and cell therapy

Introductory Message from the Chair

Ryozo Nagai, MD, PhD
Director, IMSJ

Gene therapy has been drawing attention since around 1990. While gene therapy for congenital immunodeficiency especially attracted attention, its development was suspended due to the issue of leukemia development as a result of mutation caused by retroviral vector insertion. Since the vector was improved and the target patients were narrowed down in the following years, this therapy began to draw attention once again. As many as a few hundred gene therapy clinical trials for various diseases, including cancer, metabolic diseases, and neurological disorders, are currently being conducted around the world. Jichi Medical University has been successful in performing a gene therapy using adeno-associated virus (AAV) vectors for a cranial nerve disease called ADCC deficiency.

As with the example of chimeric antigen receptor (CAR)-T cell therapy which uses the patient's T cells to produce CARs to attack lymphoma cells, cell therapy has recently become feasible. Accordingly, we asked the following professors of Jichi Medical University to give a lecture on the following topics: Keiya Ozawa, MD, PhD, Professor Emeritus and Visiting Professor, on Gene therapy comes of age: focusing on CAR-T cell therapy and Takanori Yamagata, MD, PhD on Progress of gene therapy for pediatric neurological disease.

Lecture I

Gene therapy comes of age: focusing on CAR-T cell therapy

Keiya Ozawa, MD, PhD
Professor Emeritus and Visiting Professor
Jichi Medical University

After the occurrence of leukemia due to insertional mutagenesis in hematopoietic stem cell gene therapy for X-SCID (X-linked severe combined immunodeficiency) using retroviral vectors, clinical trials of gene therapy remained stagnant for many years. However, clinical gene therapy has been revived worldwide, because a number of successful clinical trials have been reported in recent several years. Hematopoietic stem cell gene therapy became safer and realistic by using self-inactivating retroviral vectors. Then lentiviral vectors were successfully utilized for hematopoietic stem cell gene therapy even in the cases of adrenoleukodystrophy that shows CNS (central nervous system) symptoms. AAV (adeno-associated virus) vector-mediated gene therapy is shown to be clinically effective in patients with Parkinson's disease, AADC (aromatic L-amino acid decarboxylase) deficiency, Leber's congenital amaurosis, hemophilia, and spinal muscular atrophy. AAV vectors are considered to be safe and are able to transduce neurons, retinal cells, muscle cells and hepatocytes efficiently. Long-term transgene expression can be obtained after single gene transfer in such non-dividing, terminally-differentiated cells using AAV vectors, and therapeutic efficacy persists for many years. Regarding cancer gene therapy, there has been increasing focus on gene-modified T cell therapy, which is divided into CAR (chimeric antigen receptor)-T cell therapy and TCR (T cell receptor)-T cell therapy. CARs are hybrid proteins consisting of an extracellular scFv (single chain fragment of variable region) of monoclonal antibodies fused to intracellular co-stimulatory signaling domains (mainly CD28 or 4-1BB), coupled with CD3z to mediate T cell activation and proliferation. CD19-targeted CAR-T cell therapy showed surprising clinical efficacy against relapsed/refractory acute lymphoblastic leukemia and malignant lymphoma. In 2017, this novel treatment was approved by FDA in USA, followed by Europe (2018) and Japan (2019). CRS (cytokine release syndrome), ICANS (immune effector cell-associated neurotoxicity syndrome), and TLS (tumor lysis syndrome) are adverse effects that appear at an early stage following the infusion of CAR-T cells. Delayed onset toxicity of CD19-CAR-T cell therapy is the serum immunoglobulin deficiency due to destruction of normal B cells (on-target, off-tumor reaction). A next promising target antigen is considered to be BCMA (B cell maturation antigen), and BCMA-CAR-T cell therapy

has been shown to be effective against multiple myeloma. Although CD19-CAR-T cell therapy brought substantial benefit to patients with B-cell malignancies, long-term follow-up revealed that survival rate gradually decreased and that clinical outcomes are not satisfactory. The main reasons for relapse after CAR-T therapy include inadequate in vivo persistence of CAR-T cells and antigen escape of tumor cells. To overcome the former problem, improving the manufacturing process of CAR-T cells is being investigated. Further, next-generation CAR-T cells are also being designed, including optimizing the molecular structure of CAR and additional modification of CAR-T cells (so-called "armored" CAR-T cells). Another important issue is that CAR-T cell therapy for solid tumors has been unsuccessful. CAR-T cell therapy for solid tumors should be combined with other therapeutic strategies. Currently, genome editing technology is rapidly progressing, and its application to gene-modified T cell therapy is being conducted; e.g. 1) TCR gene knockout for allogeneic (universal) CAR-T cell therapy, 2) targeting a CAR to the TRAC (TCR alpha constant) locus in CAR-T cells to enhance anti-tumor efficacy, and 3) PD-1 gene knockout of CAR-T cells (local immune checkpoint blockade) to increase its cytotoxic activity.

As described above, there are still many issues to be solved in the field of gene therapy, and a serious problem in medical economics is that gene therapies recently approved are extremely expensive.

Lecture Ⅱ

Progress of gene therapy for pediatric neurological disease

Takanori Yamagata, MD,PhD
Professor
Department of Pediatrics
Jichi Medical University

Gene therapy using adeno-associated virus (AAV) vector has developed for several child neurological diseases, and some have moved to clinical use. Especially, treatment for spinal muscular atrophy (SMA) were approved as drug. We performed clinical study of gene therapy for AADC deficiency and are working to develop gene therapy for several diseases.

In patients with aromatic L-amino acid decarboxylase (AADC) deficiency, a decrease in catecholamines and serotonin levels in the brain leads to developmental delay and movement disorders. The beneficial effects of gene therapy in patients with AADC deficiency have been reported from Taiwan. We conducted a study for eight patients (age of 4 to 19 years). Seven patients were severe phenotype who were not capable of voluntary movement or speech, and one girl with a moderate phenotype who could walk with support. The patients received a total of 2×10^{11} vector genomes of AAV vector harboring AADC gene via bilateral intraputaminal infusions. Positron emission tomography with 6-[^{18}F]fluoro-L-m-tyrosine, a specific tracer for AADC, showed a persistently increased uptake in the putamen at six months and two years after the treatment. At two to five years after gene therapy, the motor function was remarkably improved in all patients. Three patients with the severe phenotype were able to stand with support, and three patients could walk with a walker. Dystonia disappeared in all patients. Patient 2 with severe phenotype started to walk with crutch after four years of therapy, and eat by herself and gastrostomy was removed. Patient 3 with the moderate phenotype could run and ride a bicycle. She could also converse fluently and perform simple arithmetic. In addition to the alleviation of motor symptoms, the cognitive and verbal functions were improved. Treatment was more effective in younger patients, and some patients suspected of having remnant enzyme activity showed better improvement.

We are developing the gene therapy for several diseases. Among them, gene therapy for Glucose transporter 1 deficiency syndrome (GLUT1DS) and Niemann-Pick disease type C1 (NPC1) showed beneficial effects for model mice. GLUT1DS is an autosomal dominant disorder caused by haplo-insufficiency of SLC2A1, and results in impaired hexose transport into the brain. Patients show intractable epilepsy and intellectual disability.

The AAV9/3 vector that expresses GLUT1 under the human GLUT1 promoter (AAV-GLUT1) was administered into ventricle of GLUT1$^{+/-}$ mice (3.25×10^{12} vg/kg). Exogenous GLUT1 was mainly expressed in endothelial cells in the brain, and partially in neural cells and oligodendrocytes. AAV-GLUT1 improved the motor function and CSF-glucose levels of GLUT1$^{+/-}$ mice without off-target effects.

NPC1 is a fatal congenital neurodegenerative disorder caused by mutations in the NPC1 gene, which is involved in cholesterol transport in lysosomes. Clinical manifestations include liver failure, pulmonary disorder and neurological deficits. The AAV9/3 vector that expresses human NPC1 under a CMV promotor (AAV-CMV-hNPC1) was injected into the left lateral ventricle and cisterna magna of Npc1$^{-/-}$ mice (total 2.7×10^{11} vg). AAV-treated Npc1$^{-/-}$ mice had an average survival of more than 28 weeks, while untreated Npc1$^{-/-}$ mice died within 16 weeks. AAV-treated Npc1$^{-/-}$ mice also showed a significant improvement in their Rotarod test performance. At 11 weeks, cerebellar Purkinje cells were preserved in AAV-treated Npc1$^{-/-}$ mice. Combined injection into both the lateral ventricle and cisterna magna achieved broader delivery of the vector to the CNS, leading to better outcomes than noted in previous reports with injection into the lateral ventricles or veins only. We are starting pre-clinical study of gene therapy for these two diseases to aim the clinical trial.

Gene therapy for SMA was approved from FDA and PMDA. One intravenous injection of AAV9 vector with SMN1 is expected to show whole life effect. SMA is caused by SMN1 deletion and show progressive cell death of spinal motor neuron. that induces progressive muscular atrophy from early infantile period and die within two years of age without respiratory support. Early treatment induces beneficial effects such as walking independently. As adverse events, transient liver dysfunction was reported because of immunological reaction for high dose vectors, and steroid administration was started before the treatment. Our patient showed transient liver dysfunction and thrombocytopenia.

Gene therapy using AAV vector is effective for some pediatric neurological and muscular diseases, but special care for adverse events are required.