Center for Gene & Cell Therapy

Division of Molecular and Medical Genetics
分子遺伝医学分野

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To promote the clinical development of gene therapy in Japan, we have been developing facilities and fundamental technologies for the manufacture of viral vectors such as adeno-associated virus (AAV) vectors and lentivirus vectors under Good Manufacturing Practices (GMP) grade. We are also developing treatments for intractable rare diseases using AAV, next-generation AAV vaccines, new cancer gene therapies, and treatments for Duchenne muscular dystrophy (DMD) using mesenchymal stromal cells (MSC).

Virus vector-related technology development

Viral vector technologies have made significant advances, particularly in the development of AAV and lentiviral vectors for gene therapy applications. AAV vectors have emerged as a leading choice for gene therapy due to their safety profile and ability to target various tissues. Novel AAV variants through improved capsid engineering have shown enhanced transduction efficiency. A nanosensor-based approach has been developed to differentiate between functional and faulty AAV vectors at the single-particle level, addressing manufacturing challenges. Significant progress has been made in AAV vector technology, particularly in manufacturing processes and applications. As for purification techniques, the combination of ultracentrifugation and ion exchange chromatography has enhanced vector purity for clinical applications. These advances in AAV vector technology are paving the way for more efficient and targeted gene therapies, with applications ranging from neurological disorders to infectious diseases.

Development of next-generation AAV vaccines

Next-generation vaccine development focuses on combining AAV and extracellular vesicle (EV) technologies to create hybrid vectors called vexosomes. These innovative vaccines aim to overcome the limitations of traditional approaches and offer improved efficacy against SARS-CoV-2 infection, as well as various other diseases, including cancer and emerging infectious diseases. Vexosomes are hybrid vectors that combine the advantages of both AAVs and EVs. AAVs provide long-term gene expression and minimal pathogenicity. EVs offer natural infection-mimicking properties and enhanced immune system interaction. This combination results in a more effective and targeted vaccine delivery system. Vexosomes can efficiently encapsulate and deliver AAV, improving antigen presentation. The hybrid nature of vexosomes can elicit stronger humoral and cellular immune responses. EV-based vaccines carrying the SARS-CoV-2 spike protein have demonstrated robust neutralizing antibody production and T cell responses in animal models. While vexosomes have great potential, sever-

al challenges need to be addressed. We are exploring methods to increase the efficiency of EV production and AAV encapsulation. We are also developing consistent and cost-effective manufacturing processes for clinical applications.

Novel treatment for DMD with MSCs

MSCs have emerged as a promising novel treatment for DMD. MSCs offer several potential benefits for DMD patients, including muscle regeneration, anti-inflammatory effects, and paracrine signaling. MSCs can differentiate into muscle cells, potentially replacing damaged dystrophin-expressing cells and improving muscle function. In addition, MSCs secrete anti-inflammatory cytokines that can modulate the immune response, reducing inflammation and protecting muscle tissue from further damage. MSCs also secrete bioactive molecules that promote tissue repair and regeneration, enhancing the survival and function of existing muscle cells. Several clinical trials are evaluating the safety and efficacy of MSC-based therapies for DMD. Early-phase trials have shown promising results, with patients exhibiting improved muscle strength, reduced fibrosis, and improved quality of life. To date, we have developed a human amnion-derived mesenchymal stromal cell (hAMSC) therapy for the treatment of DMD in collaboration with Kaneka Corporation, which has recently started a clinical trial. While MSC therapy shows significant promise for DMD treatment, challenges still remain, including ensuring consistent cell production, preventing immune rejection, and maximizing cell engraftment and survival in dystrophic muscle. Ongoing research aims to address these hurdles and enhance the potential of MSCs to effectively treat DMD.

Development of gene therapy using lentiviral vectors

In recent years, *ex vivo* gene therapy, chimeric antigen receptor (CAR) T-cell therapy has been approved for the treatment of hematological malignancies, including leukemia and malignant lymphoma, and its use is increasing due to its high efficacy. CAR-T cells are genetically modified T cells that bind and kill leukemia cells via the transduced CAR and mainly produced using lentiviral vectors. We are working to develop next-generation CAR immune cell therapy by overcoming the problems of current autologous CAR-T cell therapy, such as insufficient persistence in the body, long production time, and low efficacy against solid tumors. In the context of i*n vivo* gene therapy for genetic diseases, lentiviral vectors that enable long-term stable gene expression are also attracting attention. Our laboratory is utilizing our expertise in optimizing AAV vector production to develop a method for producing lentiviral vectors that can be administered *in vivo*.

Publications

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