Guest editorial: recent progress in gene therapy

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After the occurrence of leukemia owing to insertional mutagenesis following hematopoietic stem cell gene therapy for severe immunodeficiencies using retroviral vectors, clinical trials of gene therapy remained stagnant for many years. However, clinical gene therapy has been revived because a number of successful clinical trials have been reported recently. For example, gene therapy of Leber's congenital amaurosis, Parkinson's disease, and hemophilia B, showed adeno-associated virus (AAV) vectors were safe and clinically effective gene delivery vehicles. AAV vectors can transduce non-dividing, terminally differentiated cells efficiently, and long-term transgene expression can be obtained after single gene transfer. Another superior gene delivery vector is the lentiviral vector, which was successfully used for hematopoietic stem cell gene therapy of X-linked adrenoleukodystrophy. Even in the case of classical hematopoietic stem cell gene therapy of severe immunodeficiencies, safety was much improved using self-inactivating retroviral vectors. Regarding cancer gene therapy, targeting technology is important to improve its efficacy. In this regard, there has been increasing focus on

chimeric antigen receptor (CAR) technology when using engineered T cell therapy for hematological malignancies. CD19-targeted CAR-T gene therapy has had surprising clinical efficacy against chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL).

In this "Progress in Hematology" issue, four excellent review articles [1–4] cover recent topics in the field of gene therapy. The first two articles deal with targeted cancer gene therapy, i.e., CAR technology [1] and mesenchymal stem cells (MSCs) with tumor-homing ability [2]. The third article describes gene therapy for hemophilia B [3], which is considered one of the best targets for AAV vector-mediated gene therapy. The last article discusses hematopoietic stem cell gene therapy, the most representative and classical gene therapy for treatment of genetic diseases [4].

Davila et al. [1] provide a review on adoptive immunogene therapy using CAR-expressing T cells for hematological malignancies. Recent clinical trials of CD19-targeted CAR-T gene therapy revealed this therapeutic strategy is promising for the treatment of relapsed/refractory B cell malignancies, including CLL, ALL, and non-Hodgkin lymphoma (NHL). Interestingly, robust and rapid anti-leukemia activity of CAR-T cells was observed in patients with B-ALL, while outcomes have been more modest in patients with CLL or NHL. Davila et al. also discuss the application of CAR technology for the treatment of multiple myeloma and acute myeloid leukemia.

Another interesting targeting technology is the use of MSCs that accumulate at tumor sites. Uchibori et al. [2] reviewed the characteristics of MSCs and their potential as cellular vehicles for targeted cancer gene therapy. Since MSCs themselves may support tumor growth, genetical manipulation such as the addition of cytokine genes or suicide genes is required to provide them with anti-cancer activity. This review also discusses the molecular

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mechanisms of MSC accumulation at tumor sites. Such information will be valuable to improve MSC-based targeted cancer gene therapy.

Hemophilia B is considered a potentially responsive target disease for gene therapy using AAV vectors. Recently, clinical efficacy was finally demonstrated by liver-targeted AAV8 vector-mediated gene therapy. Patel et al. [3] describe the history of hemophilia gene therapy and recent successful clinical gene therapy using a single systemic administration of a self-complementary AAV vector to deliver an optimized factor IX expression cassette to the liver. However, further improvement is needed to reduce the risk of liver inflammation caused by immune responses against AAV capsid proteins. In addition, clinical efficacy has only been observed in patients who are negative for neutralizing antibodies against AAV particles. Thus, further measures should be developed to allow AAV vectors to escape neutralizing antibodies. Hopefully, this therapeutic strategy can be applied for other protein-supplement gene therapies in the future.

Hematopoietic stem cell gene therapy is one of the most orthodox approaches of this innovative treatment. Stem cells are considered ideal targets, but are very difficult to manipulate genetically. Insertional mutagenesis has often been observed when using retroviral vectors, and the development of leukemia in patients with X-linked severe combined immunodeficiency (X-SCID) suppressed further clinical research in this field of gene therapy. However, long-term observation of patients who underwent hematopoietic gene therapy revealed that clinical outcomes appeared to be better than patients receiving allogeneic

hematopoietic stem cell transplantation. Since then, the method of genetic transduction of stem cells has also been improved. Candotti [4] reviews the clinical experience of gene therapy for primary immunodeficiency and discusses the progress and future development of this promising medical technology.

Clinical gene therapy was a lively and growing field in the 1990s, but became stagnant in the 2000s. However, it is now undergoing revival in the 2010s. I hope that these review articles provide readers with valuable information on the current trends of gene therapy and that young hematologists will enter this exciting field and contribute to the development of innovative treatments for intractable diseases.

Conflict of interest K.O. is professor of the Corporate-Sponsored Research Division [Division of Immuno-Gene and Cell Therapy (Takara Bio), Jichi Medical University].

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