Corporate Sponsored Research Program

Project Division of Oncolytic Virus Development

ウイルス療法開発寄付研究部門

Project Professor Minoru Tanaka, M.D, Ph.D.

特任教授 博士(医学) 田 中 実

We have been conducting basic research and clinical projects to devise oncolytic virus therapies for solid cancers, including glioblastoma, olfactory neuroblastoma, and malignant pleural mesothelioma. We focus on oncolytic virus drug manufacturing processes, including scale-up, purification, filling, quality and stability testing, and characterization, as well as the development of next-generation oncolytic virus drugs to contribute to the advancement of oncolytic virus therapy in Japan.

Introduction

Our division was established as an endowed division by Denka Company Limited. We work in close conjunction with the laboratory of Innovative Cancer Therapy. Oncolytic viruses are genetically modified to replicate in and kill cancer cells while leaving normal tissues unharmed. The genetic modification of the viruses also grants them the ability to elicit anti-cancer immunity through multiple mechanisms of the patient's immune system. Genetically engineered, conditionally replicating herpes simplex viruses type 1 (HSV-1) are promising therapeutic agents for solid cancers. Our division focuses on process development and scale-up of oncolytic HSV-1 production.

A triple-mutated, third-generation oncolytic HSV-1, G47Δ, teserpaturev.

We developed a triple-mutated, third-generation oncolytic HSV-1, G47Δ, teserpaturev that has triple mutations within the viral genome. A phase II clinical trial of G47Δ was conducted since 2014 in patients with glioblastoma. In June 2021, G47Δ was approved as the world's first oncolytic virus drug for malignant gliomas. Upon commercial distribution, the oncolytic virus therapy using G47Δ (Delytact®) for patients with malignant glioma started at IMSUT hospital in November 2021. Clinical trials were also conducted for malignant pleural mesothelioma and olfactory neuroblastoma. In mesothelioma, the safety of G47Δ was confirmed, while for olfactory neuroblastoma, the recruitment of patients has been completed, and data analysis is currently ongoing.

Production of clinical-grade oncolytic HSV-1

We excel at producing master virus seed stocks (MVSS) and subsequent production of working virus seed stocks (WVSS): free of contamination, replication-competent (high titer), identity, purity, and stability. We begin with selecting cell lines for adherent or suspension culture growth, optimization of media and buffers, cell lysis, and purification of oncolytic HSV-1. We performed G47Δ genome structure analysis, stability tests, and preclinical safety evaluation. Clinical-grade G47Δ products were prepared at the Therapeutic Vectors Development Center, IMSUT hospital, with Good Manufacturing Practice (GMP). The Therapeutic Vectors Development Center has been maintained to meet the current GMP standard through regular validation of equipment and produc-

tion and an ISO9001:2015-certified quality management system. We continue to optimize oncolytic HSV-1 production to improve their safety, efficacy, and manufacturability for scale-up.

Clinical Sample Analysis and Mechanistic Insights

Through the analysis of clinical samples, including blood and pleural effusion from patients enrolled in our trials, we are investigating immune response dynamics using advanced genomic and transcriptomic approaches. These analyses focus on identifying patterns of change in the expression levels of immune-related genes before and after treatment, with particular interest in significant shifts, such as tenfold or greater changes. By continuously deepening our understanding through these studies, we aim to generate insights that will contribute to the development of novel oncolytic virus products incorporating additional immunomodulatory molecules to enhance antitumor immunity.

A recombinant herpes simplex type 1 with human IL-12 expression, T-hIL12

One of the advantages of HSV-1 is its capacity to incorporate large or multiple transgenes within the viral genome. Incorporating transgenes encoding immunomodulatory molecules into G47Δ can enhance its ability to trigger anti-cancer immunity. T-hIL12 is a G47Δ-based recombinant HSV-1 that expresses human interleukin-12 (IL-12). This IL-12-mediated anti-tumor immunity is thought to be T cell-mediated. We started a phase 1/2 clinical trial of T-hIL12 in patients with malignant melanoma in January 2020 jointly with Shinshu University. Phase 2 part of this trial is ongoing. In the ongoing phase II part, we are focusing on the collection of comprehensive data on efficacy and safety in patients with malignant melanoma. Early findings suggest that T-hIL12 effectively elicits a T cell-mediated immune response, underscoring its potential as an immunotherapeutic agent for solid tumors.

A recombinant herpes simplex type 1 with human bevacizumab expression, T-BV

Phase II trials of G47Δ in glioblastoma showed efficacy and safety, but cases of temporary brain edema were observed during the induction of anti-tumor immunity by G47Δ. To further improve the safety of viral therapy for brain tumors, we have developed T-BV, a G47Δ-based recombinant HSV-1 expressing bevacizumab that can reduce brain edema without systemic administration of bevacizumab. We have produced clinical-grade T-BV, and the protocol for the first-in-human (FIH) phase I clinical trial has been draft. We expect to start the clinical trial in the near future.

Future Directions

Building upon this year's progress, our division aims to advance ongoing clinical trials, including the completion of data analysis for olfactory neuroblastoma and the initiation of FIH trials for T-BV. We will also focus on further optimizing automated manufacturing processes and expanding the clinical applications of oncolytic HSV-1. These efforts align with our overarching goal of increasing the availability and accessibility of oncolytic virus therapies in Japan.