Development of next-generation subunit vaccines using AAV virus-like particles

Takashi Okada／The University of Tokyo

Rabies is an extremely serious zoonotic disease with a nearly 100% fatality rate once symptoms appear, with approximately 60,000 people dying from it annually, mainly in Asia and Africa. While there have been no reported domestic cases in Japan for several decades, the risk of imported cases always exists in today's globalized world, making vaccination essential for national security and bioterrorism defense. Current rabies vaccines have limitations, including complex manufacturing processes, the need for multiple doses, and high costs. The development of a new vaccine modality that is safe, affordable, rapidly scalable, and that can induce long-term immunity is an urgent international priority. This research aims to address these challenges by developing a next-generation rabies vaccine using adeno-associated virus (AAV) virus-like particles (VLPs). This system uses an AAV-derived capsid but is a VLP, not a gene delivery vector. Compared to conventional inactivated vaccines, this approach aims to reduce dosing frequency and simplify manufacturing. AAV capsid-based nucleic acid-encapsulated VLPs contain only the minimum necessary viral genome, i.e., the nucleic acid sequence almost entirely encoding an antigen. Virus-derived sequences are minimized to potentially reduce the risk of genome integration, while retaining AAV's advantages, including high stability and long-term immunity induction. Furthermore, this research aims to develop a safe and effective next-generation rabies vaccine based on AAV-VLP technology that induces long-term immunity with a single dose, comparable to that achieved with repeated administration of conventional inactivated vaccines. In detail, we will manufacture and optimize a nucleic acid-encapsulated VLP vaccine expressing the rabies virus G protein and evaluate its potential for inducing long-term immunity with a single dose in preclinical studies. In the efficacy evaluation, we will conduct a challenge trial using the rabies virus in rodents (mice) to demonstrate the effect of preventing both infection and disease progression in the vaccinated group. Furthermore, we will confirm the ability to induce neutralizing antibodies in medium-sized animals using non-rodent animals (rabbits). Progression to clinical trials will be determined based on preclinical efficacy and safety data. Ultimately, we aim to establish this technology as a vaccine platform, creating a system that enables the rapid vaccine development and scalable production and supply of vaccines not only for rabies but also for emerging and re-emerging infectious diseases. In addition, as part of our efforts toward creating next-generation technologies, we will also begin in parallel the creation of modified capsids that can evade AAV-neutralizing antibodies, both naturally present and those produced by vaccination.