Development of Novel ALK2 Inhibitor for FOP

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder, occurring in only one in 2 million people. Its onset occurs during childhood and it is progressive and intractable: there is, thus far, no effective treatment or drug-delivery method. In patients with FOP, bone and cartilage form in muscles throughout the body ("ectopic ossification") -- that is, in muscular membranes, tendons, ligaments-- after tissue injury or inflammation.

This fibrodysplasia is induced by constitutively active mutations of the ALK2 (ACVR1) gene, a type I receptor for bone morphogenetic proteins (BMPs). We have already filed an application for a patent involving the use of novel ALK2 inhibitors to treat FOP; we have also completed a structure activity relationship (SAR) study. Our present proposal is to develop RK783 for the clinical study. Drugs used to treat FOP should be administered orally, because percutaneous injection entails the risk of inducing ectopic ossification. However, there are as yet no ALK2 inhibitors that can be administered orally. Small molecule inhibitors may be more effective than antibodies to ALK2 or activin, because of their efficient distribution into muscular tissues. Our preclinical candidates (RK783) suppressed BMP signals at the cellular level in cultured cells, including iPS cells from an FOP patient. They also showed efficacy in FOP model mice, and had excellent pharmacokinetic (PK) profiles for oral administration.

In this FOP project we will focus first on non-GLP exploratory toxicity studies of the candidate, including a 14-day repeated-dosing toxicity study in rats and a toxicokinetic (TK) study, and then we will conduct GLP safety assessments.

Children with FOP depend heavily on their families because their physical activities are severely limited: they must strictly avoid injury (even tissue lesions caused by injections), infection, and inflammation. We anticipate that the development and application of our novel ALK2 inhibitor(s) will result in significant improvements in the quality of life of FOP patients and their families.