27O-ISMS33 **Discovery of Novel Spiroindoline Derivatives as Selective Tankyrase Inhibitors**

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The canonical Wnt pathway plays an important role in embryonic development, adult tissue homeostasis, and cancer. Germline and somatic mutations of various Wnt pathway components, such as Axin, APC, and β-catenin, contribute to oncogenesis. Inhibition of the poly(ADP-ribose) polymerase (PARP) catalytic activity of the tankyrases (TNKS1 and TNKS2) is known to reduce the Wnt/β-catenin signal by preventing PARsylation-dependent degradation of Axin, a negative regulator of Wnt/β-catenin signaling.

To explore the consequences of tankyrase and Wnt pathway inhibition in cancer, we searched for a small molecule inhibitor of TNKS1/2 with suitable physicochemical properties and pharmacokinetics.

Starting from a phenylpiperazinyl-5,6,7,8-tetrahydroquinazolinone derivative [a high-throughput screening hit of the Chemical library provided by Drug Discovery Initiative (DDI), the University of Tokyo, we discovered the spiroindoline derivative, RK-287107, which is a potent TNKS1/2 inhibitor (TNKS1/ 2 $IC_{50:}$ 14.3/ 10.6 nM) that has 2,000-fold selectivity against PARP-1 enzyme and inhibits Wnt signal (TCF reporter activity, IC_{50} 43 nM) and cell proliferation (GI_{50} 1.6 μM) of human colorectal cancer DLD-1 and COLO-320DM cells, respectively. Moreover, this compound has demonstrated moderate efficacy in a mouse COLO-320DM xenograft model with good pharmacokinetics and low ratio of P-glycoprotein-mediated efflux to avoid the efflux from intestine and cancer cells. These observations indicate that RK-287107 is a promising lead compound for development of tankyrase inhibitors as novel anticancer drugs.