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Cytosol-penetrating antibody technology for targeting intracellular oncogenic Ras mutants

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Ras proteins (KRas, HRas, and NRas) are small GTPases that function as molecular switches at the inner plasma membrane by alternating between GTP-bound active forms (Ras-GTP) and GDP-bound (Ras-GDP) inactive forms. Oncogenic mutations in Ras proteins, predominantly found at G12, G13, and Q61 residues, impair the GTPase activity rendering the mutants persistently GTP-bound active form, thereby promoting tumorigenesis and tumor malignancy. Oncogenic Ras mutants, frequently detected in human cancers, are high-priority anticancer drug targets. However, direct inhibition of oncogenic Ras mutants with small molecules has been extremely challenging. In this talk, I will present the development of a human IgG1 format antibody, named iMab (internalizing & protein-protein interaction (PPI) interfering monoclonal antibody), which directly targets the intracellularly activated GTP-bound form of various oncogenic Ras mutants after internalization in to the cytosol of living cells. iMab specifically binds to the PPI interfaces between activated Ras and effector proteins such as Raf and PI3K to block the associations, thereby suppressing downstream signaling and exerting anti-proliferative effects in a variety of tumor cells harboring oncogenic Ras mutants. When systemically administered, an iMab variant with an additional tumor-associated integrin binding moiety for tumor tissue targeting significantly inhibited the *in vivo* growth of oncogenic Ras-mutated tumor xenografts in mice, but not wild-type Ras-harboring tumors. Our results demonstrate the feasibility of developing therapeutic antibodies for direct targeting of cytosolic proteins that are inaccessible using current antibody technology.

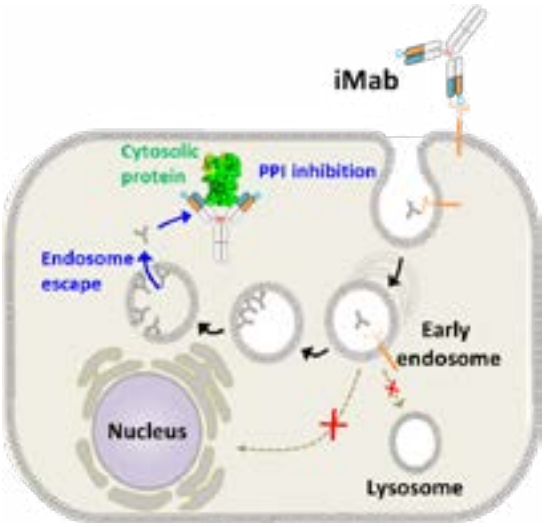

Figure 1 Schematic depicting the mechanism of action of iMab.

Biography

Yong-Sung Kim has been a Professor in Department of Molecular Science and Technology at Ajou University, Korea since 2004. He received his BSc in Food Science and Technology from Seoul National University in 1996. He obtained his MSc in Biotechnology in 1998 from KAIST and PhD in Pharmaceutical Sciences in 2002 from the University of Colorado, Denver. After obtaining the PhD degree, he joined the lab of Prof. K. Dane Wittrup at MIT as a Post-doc for protein and antibody engineering using yeast surface display. He spent one year (2010-2011) during his Sabbatical at Genentech Inc. (SF, USA), where he worked with scientists at Department of Molecular Oncology and Antibody Enginnering. His research focuses on development of next-generation antibody platform technology for potent anti-cancer therapeutics, including heterodimeric Fc-based bispecific antibody, solid tumor-penetrating antibody, and cytosol-penetrating antibody to address cytosolic proteins. In August of 2016, he co-founded ORUM Therapeutics Company with Dr. Sung-Joo Lee for the commercialization of cytosol-penetrating antibody technology.

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