

세미나 초록

성명	박창식
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발표 주제	LCB84, a TROP-2-targeted ADC, for treatment of solid tumors that express TROP-2
발표 내용	<p>LCB84 is a human Trop-2–targeting antibody drug conjugate (ADC) composed of monomethyl auristatin E (MMAE) as payload and the Hu2G10 (by Mediterranean Theranostic) humanized IgG1 antibody that selectively targets the ADAM10-activated Trop-2 protein selectively expressed in transformed cancer cells (1). LCB84 was prepared using ConjuAll™, a proprietary site-directed conjugation technology of LegoChem Biosciences, which incorporates a conjugation ‘handle’ joined by enzymatic prenylation to a specifically engineered recognition sequence (CaaX) on antibody light chains. This conjugation handle facilitates simple versatile chemical conjugation to the linker-payload. A proprietary plasma-stable cleavable linker that is recognized and cleaved by a cancer-associated lysosomal enzyme, β-glucuronidase, was used to enable efficient and traceless payload release in a cancer-specific manner. LCB84 has been evaluated for anti-tumor activity and showed superior anticancer efficacy in triple negative breast cancer (TNBC), pancreatic ductal adenocarcinoma (PDAC), gastric cancer and non-small cell lung cancer (NSCLC) cell line-derived xenograft (CDX) models compared to the ADC competitors Trodelvy and DS-1062. The LCB84 treatments were well tolerated, with no changes in body weight compared to control animals, for all dosing groups. LCB84 has robust cross-reactivity against primate Trop-2, which allows rigorous toxicity studies in monkeys. Remarkably, preliminary toxicity studies using cynomolgus monkeys showed that LCB84 is well tolerated, with calculated therapeutic index (TI, MTD/MED) of ~30 for single dosing and ~48 for repeat dosing. In conclusion, LCB84 is highly effective against Trop-2-positive CDX models in mice at doses that are well tolerated in mice and in primate models. Use of this proprietary plasma-stable cancer-selective linker technology and the Hu2G10 anti-Trop-2 monoclonal antibody that targets cancer-activated Trop-2 has led to a greatly improved next generation ADC for the treatment of various Trop-2–positive solid cancers including TNBC, PDAC, NSCLC, CRC and gastric cancer.</p> <p>(1) M. Trerotola et al., Trop-2 cleavage by ADAM10 is an activator switch for cancer growth and metastasis. <i>Neoplasia</i> 23, 415-428 (2021).</p>