ISU104, a Fully Human Antibody Targeting a Specific Epitope on the ErbB3, Displays Potent Inhibition of Tumor Growth in Multiple Xenograft Tumor Models

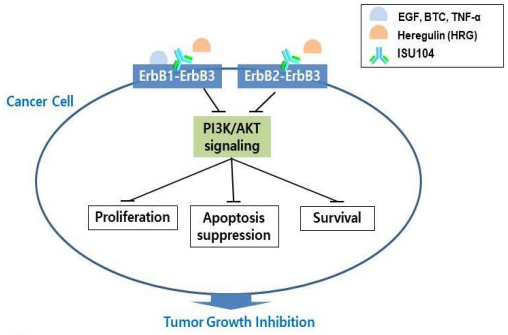
Miyoung Kim, Youngmi Hur, Mirim Hong, Sohyeon Seo, Heynjeong Lim, Kyungyong Kim, Youngsoo Sohn, Seung-Beom Hong, Donggoo Bae
ISU Abxis, Sungnam-si, Gyeonggi-do, The Republic of Korea

AACR, 2018
#5937

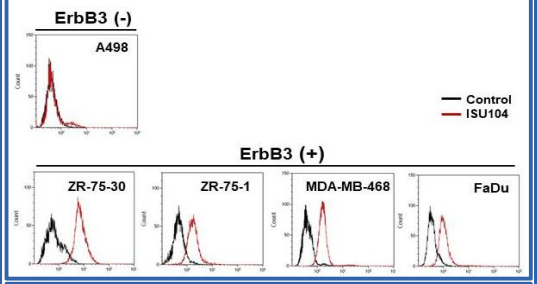
Abstract

- Members of the epidermal growth factor receptor family (ErbB family) are known as potent mediators in the development and progression of cancer. Activated ErbBs recruit various adaptors and signaling molecules through the phosphorylated cytoplasmic domain, which further leads to activation of downstream oncogenic signaling pathways. There is approved therapeutics for ErbB1 (EGFR) and ErbB2 (HER2) in the treatment of human cancers, while monoclonal antibodies targeting ErbB3 are just undergoing clinical trials.
- ISU104 is a fully human anti-ErbB3 antibody isolated from phage display antibody library. We performed the hydrogen/deuterium exchange mass spectrometry (HDX-MS) analysis with ErbB3 extracellular domain and ISU104, and that indicated that ISU104 mainly binds with domain 3 and weakly interact with domain 1 of ErbB3.
- The binding property of ISU104 induced dose-dependent inhibition of ligand (heregulin, HRG) binding, blocking of dimerization of ErbB3 with other ErbBs and subsequently inactivated the downstream signaling of ErbB3. And also, ISU104 occasioned internalization of ErbB3 from plasma membrane, and downregulated the expression level of ErbB3.
- We demonstrated the biological effect of ISU104 in several ErbB3-expressing cancer cell lines including head and neck squamous-cell carcinoma (HNSCC) and breast cancers. ISU104 completely suppressed the HRG-induced ErbB3/AKT phosphorylation, reduce cell proliferation and survival.
- Next, we evaluated efficacy of ISU104 in multiple xenograft models. Mice were treated with 10 mg/kg of ISU104 twice weekly. ISU104 regressed tumor growth in FaDu HNSCC model, and showed more than 70% tumor growth inhibition (TGI) in CAL27 (HNSCC), BxPC3 (pancreatic cancer), MDA-MB-468 (breast cancer), A549 (lung cancer), BT474 (breast cancer) models.
- Our results suggest that ISU104 effectively blocks activation of ErbB3 and the downstream pathway by ErbB3, and may provide clinical benefit to ErbB3-activated patients.

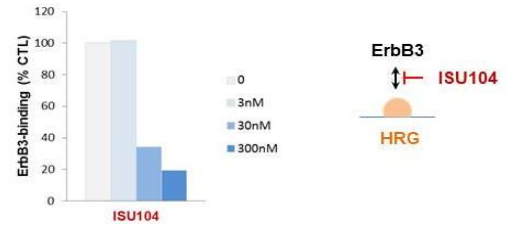
Mechanism of Action (MOA) : ISU104



Specific Binding of ISU104 to the ErbB3-Expressing Cancer Cell Lines

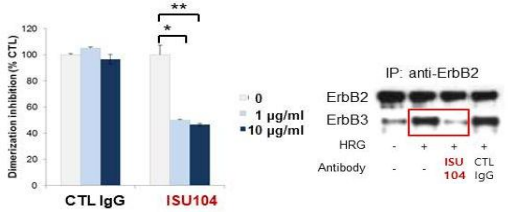


Inhibition of HRG binging to ErbB3



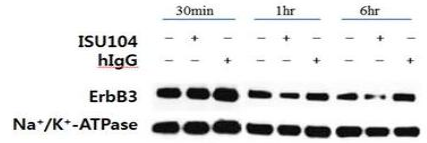
Inhibition of ErbB2/ErbB3 Dimerization

- ISU104 can inhibit HRG induced ErbB3-ErbB2 dimer formation in ZR-75-30 breast cancer cells



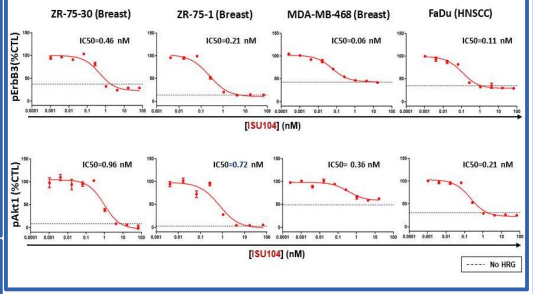
Downregulation of ErbB3 Expression

- ISU104 down-regulates ErbB3 in MDA-MB-468 breast cancer cells



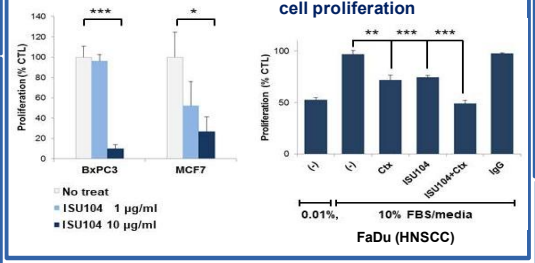
Inhibition of HRG-Dependent Signaling

- Potent inhibition of ligand (HRG)-stimulated phosphorylation in multiple cancer cell lines



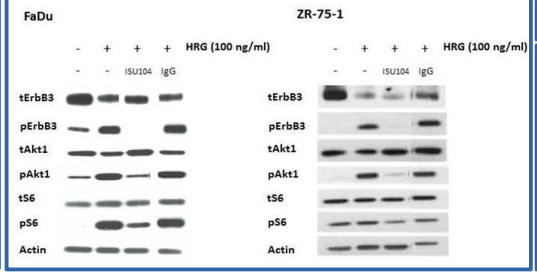
Inhibition of HRG-Dependent & Independent Proliferation

- ISU104 can inhibit HRG-stimulated cell proliferation
- ISU104 inhibited serum-mediated proliferation
- Combination with Cetuximab futhur suppressed cancer cell proliferation



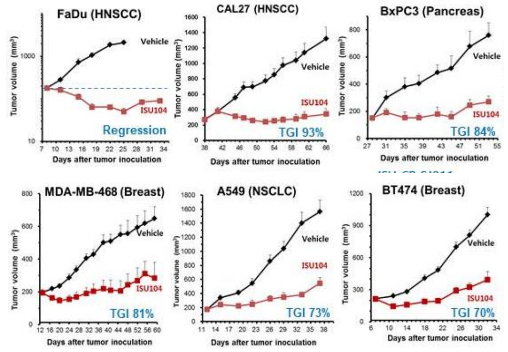
Inhibition of HRG-Dependent Survival Signaling

- ISU104 inhibits HRG-dependent survival signaling in FaDu HNSCC, ZR-75-1 breast cancer cells

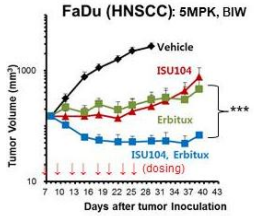


Suppression of Tumor Growth

- ISU104 inhibits or regresses tumor growth in the various xenograft models



- Combination of ISU104 with Erbitux regresses tumor growth in FaDu xenograft models



Summary

- ISU104 (anti-ErbB3) blocks ligand-dependent ErbB3 activation and inhibits dimerization of ErbB3 with ErbB1 or ErbB2
- ISU104 inhibits tumor growth in various xenograft models
- ISU104 enhances anti-tumor activity of Erbitux (anti-EGFR)
- ISU104 would be used for the treatment of cancer as a single agent or in combination with ErbB1 or ErbB2–targeted therapies

Acknowledgements

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI16C0528)