



ABT-414, an ADC Targeting a Tumor-Selective EGFR Epitope

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Marketed EGFR antibodies are unsuitable for antibody–drug conjugate (ADC) development because their significant binding to normal tissue causes on-target toxicities. ABT-414, an ADC that selectively targets tumor cells and shows minimal binding to normal tissues, potentially inhibits the growth of EGFR-positive xenograft tumors, including those expressing the EGFRde2-7 mutant form common to glioblastoma multiforme. ABT-414 combines with standard-of-care treatment radiation/temozolomide providing significant therapeutic benefit in a glioblastoma xenograft model. ABT-414 has now advanced to phase I/II clinical trials in glioblastoma patients and objective responses have been observed in a disease setting where novel treatments are urgently needed.

Mechanism of Acquired Resistance to ERK Inhibitor

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Constitutive activation of the RAS–ERK pathway is frequently observed in human cancers and is associated with high rates of cancer cell proliferation. Recently, new ERK inhibitors were identified and shown to be active in cancer cell lines with activated RAS–ERK pathway. Here, Jha, Morris, and colleagues found that prolonged treatment of HCT-116 with SCH772984, a selective ERK inhibitor, induced acquired resistance to SCH772984 through acquisition of a mutation in ERK. Interestingly, the mutation was not in the “gatekeeper” residue, as commonly found with other kinase inhibitor-resistant models. These findings suggest potential mechanisms of resistance to ERK inhibitors that are currently in clinical trials.

An HRE-Binding Py-Im Polyamide Impairs Hypoxic Signaling in Tumors

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Targeting angiogenesis is a promising therapeutic strategy, but the available therapies grant only modest improvement in patients' survival. One of the main setbacks of antiangiogenic therapies is an induction of hypoxic signaling in the treated tumors. Hypoxic signaling and its main regulator, hypoxia-inducible factor-1 (HIF-1), negatively affect tumor progression, drug resistance, and tumor angiogenesis. Here, Szablowski and colleagues show that a DNA-binding molecule can impair the hypoxic signaling in tumors, inhibit angiogenesis, reduce perivascular tumor cell survival, and inhibit prometastatic and proangiogenic gene expression.

Novel Fentomedicine Molecules Also Effective for Targeted Radiotherapy

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Discovery of new drugs that directly target cancerous cells and tumor tissues is highly desirable. A new class of non-platinum-based compounds, discovered through studies in fentomedicine (FMD), recently has been found to be effective in inhibiting cancer cell growth *in vitro* and *in vivo*. This study further reveals the radiosensitizing effects of these FMD compounds on various preclinical cancer models when combined with ionizing radiation. Importantly, the compounds themselves induce no or little radiotoxicity toward normal cells or tissues. These compounds are therefore effective hypoxic radiosensitizers that have the potential to be translated into clinical trials for targeted radiotherapy of multiple cancers.