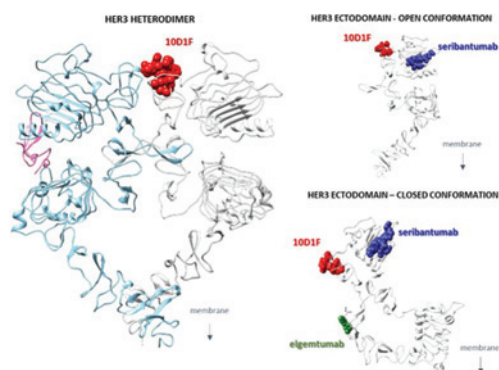


MOLECULAR CANCER THERAPEUTICS

HIGHLIGHTS

Highlights of This Issue

10DF1, an Anti-HER3 Antibody that Uniquely Blocks the Receptor Heterodimerization Interface, Potently Inhibits Tumor Growth Across a Broad Panel of Tumor Models

Thakkar *et al.* | Page 490

The Human Epidermal Growth Factor Receptor 3 (HER3) signals through forming heterodimers with EGFR or HER2 in order to activate the PI3K pathway. To date, targeting HER3 with antibodies has shown sub-optimal results. To combat this, Thakkar and colleagues designed a picomolar antibody (10DF1) that targets HER3 at the heterodimerization interface. 10DF1 potently inhibited heterodimerization with EGFR and HER2 and restricted PI3K signaling. 10DF1 showed *in vivo* tumor growth inhibition in mouse models of gastric, lung, head and neck, and ovarian cancers. 10DF1 therefore represents a novel class of anti-HER3 neutralizing antibodies with clinical promise in multiple cancer indications.

ERK Inhibitor LY3214996 Targets ERK Pathway-Driven Cancers: A Therapeutic Approach Towards Precision Medicine

Bhagwat *et al.* | Page 325

Despite advances in BRAF and MEK inhibitors, many patients develop resistance within one year. In the majority of cases, this resistance is due to ERK reactivation. In this manuscript, Bhagwat and colleagues outline the preclinical activity of LY3214996, a potent, selective, ATP competitive ERK inhibitor designed to overcome this resistance. LY3214996 inhibited subcutaneous xenograft tumors with BRAF, KRAS, NRAS, and MEK mutations as well as patient-derived, vemurafenib resistant colorectal cancer model. LY3214996 also demonstrated a synergistic effect in combination with a pan-RAF inhibitor (LY3009120). Continued clinical study (NCT02857270) will elucidate LY3214996 as a clinical therapy for patients with ERK pathway alterations.

Dual-mechanism ERK1/2 Inhibitors Exploit a Distinct Binding Mode to Block Phosphorylation and Nuclear Accumulation of ERK1/2

Kidger *et al.* | Page 525

ERK1/2 inhibitors (ERKi) undergoing clinical trials have two distinct mechanisms of action. Catalytic ERKi inhibit the ERK1/2 catalytic activity, while dual mechanism ERKi also prevent ERK phosphorylation by MEK. In this manuscript, Kidger and colleagues determine the functional consequences intrinsic to the mechanisms of five ERK inhibitors (GDC-0994, BVD-532, LY-3214996, SCH772984, and Compound 27). Catalytic inhibition coincided with nuclear accumulation of ERK. The dual inhibitor SCH772984 demonstrated an increased modulation of ERK1/2-dependent gene expression than the catalytic ERKi GDC-0994 and prevented nuclear accumulation. The authors conclude these differences may have implications in pathway rebound following feedback relief.

Therapeutic Breast Reconstruction using Gene Therapy Delivered IFN- γ Immunotherapy

Davis *et al.* | Page 697

Breast reconstruction, performed after mastectomy, frequently utilizes autologous tissue that is removed and reattached using microvascular anastomoses. Davis and colleagues hypothesized that the period of time in which the tissue is *ex vivo* presents a unique opportunity for modifying genetics without systemic exposure. In this manuscript, they demonstrate that delivering the IFN γ gene to autologous tissue *ex vivo* prevented loco-regional recurrence in two breast cancer lines in rat models. The resulting local IFN γ release stimulated M1 macrophages within the tumor environment. Future translation into patients would potentiate combining reconstruction with a molecular, localized immunotherapy, and is termed 'Therapeutic Breast Reconstruction'.