



Engineering of Dual-Targeting Anti-FGFR2/3 Antibodies

Yin *et al.* _____ Page 2270

This study engineered an existing antibody to discriminate between FGFR isoforms. While inhibiting FGFR2 or FGFR3 does not disrupt tissue homeostasis, blocking FGFR1 or FGFR4 carries a greater safety risk. R3Mab, an anti-FGFR3 antibody, was initially modified to bind tightly to FGFR3 and FGFR2 and moderately to FGFR4. Based on X-ray crystallographic data, it was further engineered to decrease FGFR4 binding affinity while retaining affinity for FGFR3 and FGFR2. The resulting dual-specific antibodies blocked FGF binding to FGFR3 and FGFR2 and displayed efficacy in mice against human tumor xenografts overexpressing FGFR3 or FGFR2. Thus, a monospecific antibody can be engineered to modify binding to closely related targets in order to expand and refine therapeutic potential.

ASCL1 Is a Target Gene of the BET Inhibitor JQ1 in SCLC

Lenhart *et al.* _____ Page 2167

This study demonstrates that small cell lung cancer (SCLC) cells are exquisitely sensitive to growth inhibition by the BET inhibitor JQ1. JQ1 treatment has no impact on MYC protein expression, but results in downregulation of the lineage-specific transcription factor *ASCL1*. SCLC cells that are sensitive to JQ1 are also sensitive to *ASCL1* depletion by RNA interference. Chromatin immunoprecipitation studies confirmed the binding of the BET protein BRD4 to the *ASCL1* enhancer, and the ability of JQ1 to disrupt the interaction. The study provides a mechanistic basis for the sensitivity of SCLC to BET inhibition, and a rationale for the clinical development of BET inhibitors in this disease with high unmet medical need.

5-HD as a Neuroprotective Drug

Chen *et al.* _____ Page 2206

This study aimed to discover potential neuroprotective drugs for paclitaxel-induced neurotoxicity. An image-based high-content platform was first developed to screen for potential neuroprotective drugs. In drug screening from compound libraries of ion channel ligands, REDOX and GABAergic ligands, 5-hydroxydecanoate (5-HD) exhibited the most significant neuroprotective effects against paclitaxel-induced neurotoxicity, both in cortical and dorsal root ganglion (DRG) neurons. In mouse behavioral tests, 5-HD restored the thermal sensitivity and alleviated mechanical allodynia induced by paclitaxel. The study establishes an image-based high-content screening platform and a protocol for verifying the neuroprotective effect *in vivo*, by which 5-HD was identified and validated as a potential neuroprotective drug for paclitaxel-induced neuropathy.

NSCLC Mouse Model Driven by *DDR2* Mutation

Xu and Buczkowski *et al.* _____ Page 2382

Genetically engineered mouse models of lung cancer are important in understanding the function of novel lung cancer oncogenes and tumor suppressor genes identified in genomic studies of human lung cancer. Further, they are important platforms for preclinical therapeutic studies. This study generated a mouse model of lung adenocarcinoma driven by mutation of the discoidin domain receptor 2 (*DDR2*) gene combined with loss of *TP53* and analyzed results to reach a conclusion that *DDR2* mutation can drive lung cancer initiation *in vivo* and provide a novel mouse model for lung cancer therapeutics studies.