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**Blockade of Specific NOTCH Ligands: A New Promising Approach in Cancer Therapy**

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**Synovial Sarcoma: Recent Discoveries as a Roadmap to New Avenues for Therapy**

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**Biallelic Mutations in BRCA1 Cause a New Fanconi Anemia Subtype**

Précis: Deleterious biallelic BRCA1 mutations predispose to a Fanconi anemia–like disorder characterized by developmental abnormalities and breast and ovarian cancer susceptibility.

**PI3′-Kinase Inhibition Forestalls the Onset of MEK1/2 Inhibitor Resistance in BRAF-Mutated Melanoma**

M.M. Deuker, V. Marsh Durban, W.A. Phillips, and M. McMahon
Précis: Treatment with PI3K inhibitors enhances the depth of response to MEK1/2 inhibition and delays the development of drug-resistant tumors in BRAF-mutated melanoma mouse models.

**Linking Tumor Mutations to Drug Responses via a Quantitative Chemical–Genetic Interaction Map**

Précis: Isogenic cell lines can be used to systematically map direct relationships between genetic alterations and drug responses and identify actionable interactions.

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### IN THE SPOTLIGHT

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### SYNTHESIS

**Synovial Sarcoma: Recent Discoveries as a Roadmap to New Avenues for Therapy**

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**Linking Tumor Mutations to Drug Responses via a Quantitative Chemical–Genetic Interaction Map**

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Aberrant Glycosylation Promotes Lung Cancer Metastasis through Adhesion to Galectins in the Metastatic Niche

N.E. Reticker-Flynn and S.N. Bhatia

Précis: Changes in glycosyltransferase activity in lung cancer cells enhance surface presentation of the carbohydrate ligand T-antigen and potentiate metastasis via increased binding to tumor-mobilized galectin-3+ leukocytes.

See commentary, p. 109

NOTCH Decoys That Selectively Block DLL/NOTCH or JAG/NOTCH Disrupt Angiogenesis by Unique Mechanisms to Inhibit Tumor Growth


Précis: Specific inhibition of JAG- or DLL-mediated NOTCH signaling using synthetic NOTCH1 decoys inhibits tumor angiogenesis via distinct mechanisms.

See commentary, p. 112

Reticker-Flynn and Bhatia found that tumor-derived IL6 induced CD11b+ galectin-3+ leukocyte mobilization from the bone marrow in a mouse model of lung adenocarcinoma. Metastatic cell lines and human non–small cell lung cancer samples exhibited increased surface presentation of the galectin-3 ligand, Thomsen-Friedenreich Antigen (T-Antigen). Elevated T-Antigen surface presentation was mediated by altered expression of the glycosyltransferases C2GnT2 and St6GalNAc4, which prevented T-Antigen glycan elongation. Restoration of T-Antigen glycan chain elongation decreased T-Antigen presentation, reduced tumor-cell galectin-3 binding, and inhibited experimental metastases in vivo. These results indicate that aberrant glycosyltransferase activities play a critical role in the early metastatic niche to promote metastatic progression of lung tumors. For details, please see the article by Reticker-Flynn and Bhatia on page 168.