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Humana Cancer Biology

The Journal of Clinical and Translational Research www.aacrjournals.org
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<th>Year</th>
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<td>1915</td>
<td>A Phase I Pharmacologic Study of Necitumumab (IMC-11F8), a Fully Human IgG1 Monoclonal Antibody Directed Against EGFR in Patients with Advanced Solid Malignancies</td>
<td>Bart Kuenen, Petronella O. Witteveen, Rita Ruijter, Giuseppe Giaccone, Aruna Dontabhaktuni, Floyd Fox, Terry Katz, Hagop Youssoufian, Junming Zhu, Eric K. Rovinsky, and Emile E. Voest</td>
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**SUSCEPTIBILITY AND PREVENTION**

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<tr>
<td>1950</td>
<td>Mesalazine Reduces Mutations in Transforming Growth Factor β Receptor II and Activin Type II Receptor by Improvement of Replication Fidelity in Mononucleotide Repeats</td>
<td>Christoph Campregger, Clemens Honeder, Heekyung Chung, John M. Carethers, and Christoph Gasche</td>
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<tr>
<td>1957</td>
<td>A High Proportion of DNA Variants of BRCA1 and BRCA2 Is Associated with Aberrant Splicing in Breast/Ovarian Cancer Patients</td>
<td>David J. Sanz, Alberto Acedo, Mar Infante, Mercedes Durán, Lucía Pérez-Cabornero, Eva Esteban-Cardenosa, Enrique Lastra, Franco Pagani, Cristina Miner, and Eladio A. Velasco</td>
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**LETTERS TO THE EDITOR**

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<tr>
<td>1968</td>
<td>Correlation of Segmented Metabolic Tumor Volume with Outcome - Response</td>
<td>Man Ki Chung, Chung-Hwan Baek, and Joon Young Choi,</td>
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ABOUT THE COVER

Human pancreatic cancer–associated fibroblasts (CAFIs) overexpress the Hedgehog receptor SMO. Here, immunohistochemical labeling highlights overexpression of Smo protein in a human primary pancreatic adenocarcinoma. Strong Smo expression is detected in stromal fibroblasts adjacent to pancreatic cancer cells. For details, see the article by Walter and colleagues on page 1781 of this issue.