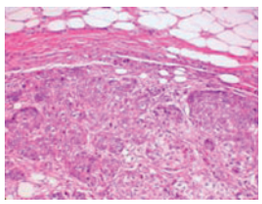
Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
AACR American Association for Cancer Research

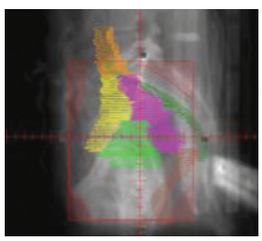
Novel Combination Therapies in TNBC



Patients with triple-negative breast cancer (TBNC) receive little benefit from cytoxic or targeted therapies currently in the clinic. To identify novel combinations beneficial to TBNC patients, Wali and colleagues evaluated 128 experimental agents for their ability to synergize with six FDA-approved drugs in reducing the viability of TNBC cell lines. While the majority of combinations were antiproliferative, only a few displayed synergy. Combinations showing this increased sensitivity were further evaluated, including comparisons of gene and protein expression. The most successful combinations included the proapoptotic drug ABT-263, the MDM2 inhibitor nutlin-3, or the bromodomain inhibitor JQ1, with paclitaxel. ABT-263 also synergized with two distinct MET inhibitors, crizotinib and XL-184, consistent with *MET* overexpression in TNBC patient tumors. These combinations are readily translatable for TBNC patients. *(Image courtesy of Wikimedia Commons.)*

Wali VB, Langdon CG, Held MA, Platt JT, Patwardhan GA, Safonov A, et al. Systematic drug screening identifies tractable targeted combination therapies in triple-negative breast cancer. Cancer Res 2017;77:566–78.

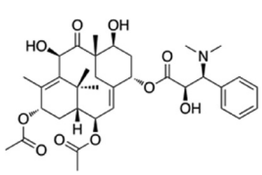
Systems Biology Approach to Radiation Therapy



Over two-thirds of cancer patients receive radiotherapy. Despite this era of precision medicine, radiotherapy dosing is prescribed based not on individual tumor biology, but in a very generic fashion. Scott and colleagues generated a genomic-adjusted radiation dose (GARD) model by integrating radiobiological mathematical modeling with a gene-expression–based radiosensitivity index, derived from the high-throughput transcriptomic profiling of 48 cancer cell lines following irradiation. They validated the GARD model on 8271 tumor samples from a diverse collection of cancer types comprising five separate radiation treated clinical cohorts. Upon multivariable analysis, the GARD was found to correlate with local control, metastasis-free survival, and overall survival in these diverse histologic cohorts based on the dose of radiotherapy delivered. If validated prospectively, GARD may enable a precision medicine approach to optimize radiotherapy doses to match the radiosensitivity of individual tumors. *(Image courtesy of Wikimedia Commons.)*

Scott JG, Berglund A, Schell MJ, Mihaylov I, Fulp WJ, Yue B, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. Lancet Oncol 2016 Dec 18. doi: 10.1016/S1470-2045(16)30648-9. [Epub ahead of print].

Actin Regulator MENA Confers Taxane Resistance

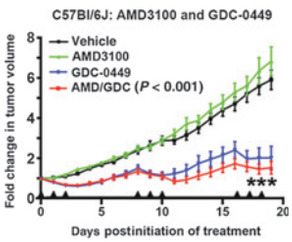


Expression of MENA^{inv}, a cancer-specific splice variant of the actin regulatory protein MENA, correlates with poor patient outcome and metastasis in several breast cancer cohorts. Oudin and colleagues now demonstrate that expression of MENA and MENA^{inv} confer taxane resistance to breast cancer cells *in vitro* and *in vivo*. MENA expression increased MAPK signaling, interfering with taxane function due to MAPK pathway-induced microtubule dynamics. Given that taxanes function via stabilizing microtubules, elevated MAPK activity in the MENA-expressing cells counteracts taxane function, conferring resistance. Combinatorial treatment of MENA and MENA^{inv} cells with MAPK inhibitors increased their sensitivity to taxanes and correlated with increased microtubule sensitivity. Thus, MENA and MENA^{inv} are not only clinically relevant drivers of cancer invasion, but also confer highly metastatic cancer cells with taxane resistance that could be overcome by combining MAPK inhibition and chemotherapy. *(Image courtesy of Wikimedia Commons.)*

Oudin MJ, Barbier L, Schäfer C, Kosciuk T, Miller MA, Han S, et al. MENA confers resistance to paclitaxel in triple-negative breast cancer. Mol Cancer Ther 2017;16:143–55.

Breaking Advances

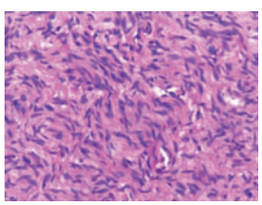
Targeting Medulloblastoma by Inhibiting SHH and CXCR4



While both the CXCR4 chemokine and Sonic Hedgehog (SHH) pathways are therapeutic targets for medulloblastoma, CXCR4 or SHH antagonists alone have shown only limited clinical efficacy. Ward and colleagues demonstrate that inhibiting both the SHH and CXCR4 pathways promoted antitumor effects in flank and intracerebellar orthotopic xenograft murine models of SHH-subtype medulloblastoma. Specifically, tumor-propagating cell function was suppressed and this suppression correlated with an increase in histone H3 lysine 27 trimethylation in the stem cell gene promoters, resulting in a decrease in expression of stem cell genes. The authors identified epigenetic regulation of a protumor cell phenotype by CXCR4. Further, the authors provide early proof of principle for the combination of SHH and CXCR4 inhibition in patients with medulloblastoma, which might also be relevant for other cancers with SHH involvement and CXCR4 overexpression. *(Image from cited article courtesy of the publisher.)*

Ward SA, Warrington NM, Taylor S, Kfoury N, Luo J, Rubin JB. Reprogramming medulloblastoma-propagating cells via combined antagonism of Sonic Hedgehog and CXCR4. Cancer Research; Published OnlineFirst December 28, 2016; doi: 10.1158/0008-5472.CAN-16-0847.

MEK Inhibition for *NF1* Plexiform Neurofibromas



Plexiform neurofibromas are slow growing peripheral nerve tumors that are a major cause of morbidity in neurofibromatosis type 1 and have no effective therapies. To evaluate MEK inhibition in plexiform neurofibromas, Dombi and colleagues conducted a phase I study of selumetinib in 24 children, and in a cross-species comparison, treated a murine model of NF1. Tumor volumes decreased by 6–47% in all children, and many responses were durable. Mouse tumors showed a similar decrease in volume, a rapid but transient decrease in levels of phospho-ERK, and decreased proliferation. The parallel murine clinical trial validates the neurofibroma animal model for selection of future targeted agents. This unique study provides a proof of principle for treatment of plexiform neurofibromas with MEK inhibition and highlights the utility of combined parallel human and mouse clinical trials. *(Image Courtesy of Wikimedia Commons.)*

Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, et al. Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. N Engl J Med 2016;375:2550–60.

Extracellular Protein Catabolism in Pancreatic Tumors

Pancreatic ductal carcinoma cells rely on scavenging pathways such as endocytosis (macropinocytosis) to obtain amino acids for metabolism. Using a perfusion-based microfluidic strategy, Davidson and colleagues performed plasma exchange to deliver stable nitrogen isotope-labeled albumin [^{15}N-MSA] to tissues in live mice. They determined that internalization and breakdown of circulating albumin contributed more free amino acids to pancreatic tumors compared with normal pancreas. Delivering albumin and other protein substrates directly into tumors, the authors observed macropinocytosis and protein catabolism *in situ* in pancreatic cancer cells, but not in adjacent, noncancerous pancreas. In addition, intratumoral inhibition of macropinocytosis decreased amino acid levels. These data suggest that pancreatic cancer cells consume extracellular proteins and that this consumption serves as an important source of amino acids for pancreatic cancer cells *in vivo*. *(Image courtesy of Wikimedia Commons.)*

Davidson SM, Jonas O, Keibler MA, Hou HW, Luengo A, Mayers JR, et al. Direct evidence for cancer-cell-autonomous extracellular protein catabolism in pancreatic tumors. Nat Med 2016 Dec 26. doi: 10.1038/nm.4256. [Epub ahead of print].

Note: Breaking Advances are written by *Cancer Research* editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.