MD Anderson Research Highlights for September 22, 2021

Featuring discoveries in breast cancer, multiple myeloma, cholangiocarcinoma, molecular imaging, gynecologic cancers and pancreatic cancer

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The University of Texas MD Anderson Cancer Center's Research Highlights provides a glimpse into recently published studies in basic, translational and clinical cancer research from MD Anderson experts. Current advances include a new method to measure breast cancer response, a new immunotherapy approach for multiple myeloma, characterization of the immune landscape of cholangiocarcinoma, a new contrast agent to improve molecular imaging techniques, and new treatment targets in breast, gynecologic and pancreatic cancers.

Residual cancer burden offers a predictive response measure across breast cancer treatments and subtypes

Residual cancer burden (RCB) is an MD Anderson-developed method to measure a breast cancer patient's response to neoadjuvant chemotherapy and to estimate the risk of future disease recurrence using a standardized approach that is incorporated into routine pathology practice. W. Fraser Symmans, M.D., worked with a team of researchers from the I-SPY Clinical Trials Consortium to investigate whether new treatments change the extent of RCB and determine what that might mean for predicting a difference in the risk of disease recurrence. Their results show that measurement of RCB was an accurate and consistent indicator of prognosis in each subtype of breast cancer. Furthermore, lowering RCB using an investigational treatment in the trial was associated with lower risk of disease recurrence compared to the standard chemotherapy. These findings indicate that RCB is a reliable measure of response from chemotherapy-based treatments that can be used to estimate a patient's residual risk of recurrence and to compare the effectiveness of different treatments. Learn more in *JAMA Oncology*.

Combination immunotherapy produces stronger immune reconstitution in multiple myeloma

Patients with multiple myeloma may benefit from immunotherapy approaches that augment their anti-myeloma immune response. To test this hypothesis, Muzaffar Qazilbash, M.D., and colleagues conducted a randomized phase II trial of an anti-myeloma vaccine, idiotype-keyhole limpet hemocyanin (Id-KLH), or a control vaccine (KLH only) in combination with vaccine-specific, co-stimulated T cells in the setting of an autologous transplant. No dose-limiting toxicities were observed. Thirty percent of patients treated with the control vaccine achieved complete remission, and 50% of patients treated with Id-KLH achieved complete remission. The gene expression analysis found that the anti-myeloma vaccine produced a stronger anti-myeloma immune response compared to the control vaccine, suggesting that the Id-KLH vaccine and adoptive immunotherapy strategies warrant additional investigation. Learn more in *Blood*.

Deciphering the immune landscape of cholangiocarcinoma

Intrahepatic cholangiocarcinoma (iCCA), a cancer of the bile ducts of the liver, lacks effective treatment options and has seen only marginal benefit from immune checkpoint inhibitors. To characterize the immune landscape of iCCA, researchers led by Fernando Carapeto, Ph.D., Behnaz Bozorgui, Ph.D., Anil Korkut, Ph.D., and Lawrence Kwong, Ph.D., performed next-generation sequencing and immune profiling on surgical iCCA samples from 96 MD Anderson patients. These samples demonstrated lower expression of immune markers in the center of the tumor relative to the periphery, indicating poor immune cell infiltration. Patients fit into four subgroups based on the expression of immune markers, with high PD-1 or LAG3 expression and low CD3/CD4/ICOS expression associated with shorter survival. Additionally, the presence of loss-of-function *BAP1* mutations resulted in increased levels of the immune suppressive marker B7H4. These findings provide a foundation for understanding the immune environment of iCCA and predicting which patients may benefit from immunotherapy. Learn more in *Hepatology*.

TRIM24 identified as key driver in metaplastic breast cancers

Metaplastic breast cancer (MpBC) is a rare subclass of triple-negative breast cancers that are marked by the presence of both epithelial and mesenchymal cancer cells within an individual tumor. MpBCs do not respond well to chemotherapy and have poor outcomes. Advances in this cancer have been limited by a lack of model systems to study the disease. According to new findings reported by Vrutant Shah, Ph.D., and colleagues, overexpression of the histone reader protein TRIM24 in murine mammary epithelia resulted in the development of tumors that closely resemble human MpBCs. Studying this new model revealed a new understanding of MpBC, including the discovery of

activated pathways regulating glycolysis, epithelial-to-mesenchymal transition and PI3K signaling. The findings suggest that TRIM24 may be a potential biomarker for MpBC and that targeting TRIM24 or the PI3K pathway may be a potential therapeutic strategy. Learn more in *Nature Communications*.

Development of novel contrast agent offers improved molecular imaging technique

Molecular imaging enables the real-time visualization of chemical and biological processes to support diagnostic and therapeutic applications. The most widespread technique, positron emission tomography (PET), offers high sensitivity but limited spatial resolution. While photoacoustic (PA) imaging is an emerging technique that can provide both high sensitivity and spatial resolution, its use is limited by currently available contrast agents. A research team led by Cayla Wood, Ph.D., Konstantin Sokolov, Ph.D., and Richard Bouchard, Ph.D., report the development of a novel PA contrast agent, called PAtrace, to address those limitations. Characterization of PAtrace in various imaging environments demonstrated improved signal strength and specificity compared to current agents. Combining PAtrace with an antibody targeting a protein abundant in ovarian cancer enabled real-time visualization of ovarian cancer cells in laboratory models. The findings suggest that PAtrace warrants further investigation as an agent for clinical PA imaging. Learn more in *Nature Communications*.

New study identifies metabolic vulnerability in treatment-resistant TNBC

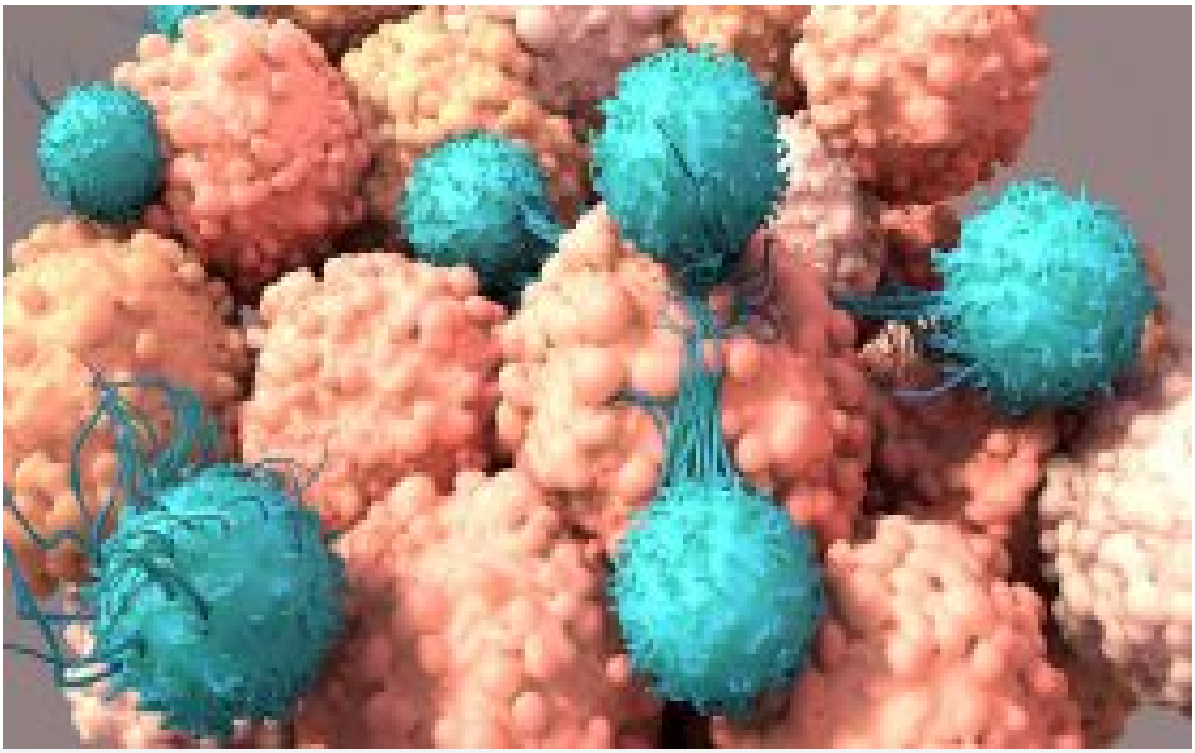
Many cancers develop a dependence on the oxidative phosphorylation (OXPHOS) metabolic pathway due to acquired genetic mutations. Researchers, led by Kurt W. Evans and Funda Meric-Bernstam, M.D., demonstrated that triple-negative breast cancers (TNBCs) are highly reliant on OXPHOS. Analyzing RNA from pre-treatment biopsies of TNBC patients who received neoadjuvant chemotherapy revealed that a higher expression of OXPHOS genes was associated with a higher risk of recurrence and death. Treatment with IACS-10759, an OXPHOS inhibitor discovered and developed by MD Anderson's Therapeutics Discovery division, inhibited tumor growth in certain TNBC subtypes. Further, combining IACS-10759 with palbociclib, a CDK4/6 inhibitor, and cabozantinib, a multi-kinase inhibitor, improved antitumor effects *in vitro* and *in vivo.* The findings suggest that inhibiting OXPHOS may be a novel approach to enhance efficacy of several targeted therapies, especially for chemotherapy-resistant patients. Learn more in *Cancer Research*.

Dose expansion study of combined PARP and AKT inhibitors shows promising treatment for breast and gynecologic cancers

Alterations in the PI3K signaling pathway are frequently implicated in various types of cancers, including breast and gynecologic cancers, making it an attractive therapeutic target. However, targeting the pathway has been challenging due to limited single-agent activity and high levels of toxicity. In a phase Ib dose expansion study led by Shannon N. Westin, M.D., researchers enrolled 38 patients with advanced and/or recurrent ovarian, endometrial and triple-negative breast cancer to test the safety of the PARP inhibitor olaparib in combination with an AKT inhibitor, capivasertib, which targets the PI3K pathway. The data showed that the combination therapy has the potential to elicit a durable response with manageable adverse events, including an impressive response in women with recurrent endometrial cancer, which is typically hard to treat with standard therapy. Researchers also conducted an extensive translational study of tumor samples before and during treatment, identifying two sets of biomarkers: one identified predictive markers associated with response to therapy, which may improve patient selection in future trials; and the other established molecular markers of resistance to the drug combination, which may offer insight into combination strategies. Learn more in *Clinical Cancer Research*.

USP21 promotes pancreatic cancer growth independent of mutant KRAS

Nearly all pancreatic cancers have activating mutations in the *KRAS* gene, which support tumor growth and maintenance. However, cancers can overcome their dependence on mutant KRAS by activating alternative pathways, rendering them resistant to therapies targeting mutant KRAS – a phenomenon called KRAS extinction. Researchers led by Pingping Hou, Ph.D., Y. Alan Wang, Ph.D., and Ronald A. DePinho, M.D., discovered that the protein USP21 can promote tumor growth independent of mutant KRAS. The researchers previously identified USP21 as a driver of pancreatic cancer, and the current findings clarify the mechanism of the protein's action. They demonstrated USP21 regulates the MARK3 protein to control macropinocytosis, a cellular process to uptake amino acids, and provide metabolic support in pancreatic cancer cells. This pathway bypasses mutant KRAS dependency, suggesting USP21 may be a novel treatment target in pancreatic cancer. Learn more in *Genes & Development*.



Media Specialist Contact

Clayton Boldt, Ph.D.

713-792-5582
crboldt@mdanderson.org

MD Anderson Public Relations Office

1-713-792-0655
publicrelations@mdanderson.org
@MDAndersonNews