Treatment Target Discovered for Some Triple-Negative Breast Cancers

New research has uncovered the role of MYCN in triple-negative breast cancer (TNBC), identifying a new avenue for investigation for a disease that currently has few therapeutic options (Sci Transl Med 2020; doi:10.1126/scitranslmed.aaw8275).

While there is currently no way to target MYCN directly, the study—conducted by researchers at Vanderbilt-Ingram Cancer Center—found that BET inhibitors are an effective treatment for MYCN-expressing TNBC. They also determined that these drugs are especially effective when combined with MEK inhibitors.

"For over a decade, a primary focus of my laboratory has been TNBC," noted Jennifer Pieterpol, PhD, the Benjamin F. Byrd Jr. Professor of Oncology and the study’s senior author.

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Life in the Time of COVID-19

The COVID-19 (Coronavirus Disease-2019) world pandemic is still in the mid-phases in most of the world. It may persist for several months, or even longer. In some geographies that ignored its early threat (Spain, Italy), COVID-19 spread rapidly and overwhelmed medical infrastructures: hospital beds, ICU beds, respirators, dialysis machines, personal protective equipment (PPE), and health care workers. This extended to areas with COVID-19 spread-enhancing features: cosmopolitan, high influx of tourism, dense populations, mass transit, poorer neighborhoods with close quarters and multigenerational families, large events (Mardi Gras in New Orleans, soccer game with 40,000 attendance in Lombardy, Italy).

In these epicenters, COVID-19 continues to infect millions and cause the deaths of tens of thousands. These figures may be underestimations because of lack of widespread testing, autopsies, and reporting. The virus is weakening world economies and large and small industries, particularly in the sectors of oil, services, tourism, transportation, sports, and the arts. It is also rapidly spreading in cities, suburbs, and small towns across the country.

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author. “We’ve had a long-standing interest in finding new treatments for this disease since, even though it only represents 15 percent of diagnosed breast cancer in the U.S., it leads to 25 percent of breast cancer mortality.”

There have been few new advances in FDA-approved treatments. While this changed with the introduction of PARP inhibitors and, more recently, the approval of atezolizumab and nab-paclitaxel, according to Pietenpol, treatment options remain limited for TNBC patients, especially those with advanced metastatic disease.

TNBC, which typically impacts younger women, is characterized by increased relapse rates, more frequent metastasis, and shorter survival compared to the other subtypes of breast cancer, according to the study authors.

“Development of targeted therapies for TNBC is challenging because of its molecular heterogeneity and lack of therapeutically targetable, high-frequency driver alterations,” they wrote. “Understanding the heterogeneity within TNBC and molecular mechanisms that contribute to the emergence of treatment-resistant, metastatic disease may inform the development of more effective therapeutics and address an unmet medical need in breast cancer.”

**Study Details**

While exploring TNBC and seeking to better understand the disease, Johanna Schafer, PhD, graduate student and first author of the study, made a serendipitous discovery. She was working on a project to figure out how to overcome TNBC cell resistance to PI3K inhibitors and noticed that many of the cells that became resistant to those inhibitors expressed MYCN, explained Pietenpol.

“From there,” she noted, “we wondered, if cells that are stressed and become resistant to drugs express MYCN, how many primary triple-negative breast cancers express MYCN? And how many after treatment? How many when they recur?”

Researchers designed the study to identify the proportion of treatment-naive (n=191), neoadjuvant chemotherapy-treated (n=115), and recurrent TNBC tumors (n=38) that express MYCN. They collected clinical specimens for immunohistochemistry (IHC) analyses at Vanderbilt University Medical Center; Instituto Nacional de Enfermedades Neoplásicas in Lima, Peru; or in conjunction with a commercial source.

“All clinical and pathologic data were retrieved under institutionally approved protocols,” the study authors explained. “Protein expression (H-scores) resulting from IHC for MYCN and MYC was determined by a pathologist and analyses were performed by researchers blinded to the patients’ medical background and treatments received.”

The researchers found that MYCN is heterogeneously expressed among a substantial fraction of primary and recurrent TNBCs. Additionally, they showed that it is expressed in an even higher number of TNBCs that do not have a pathological complete response after neoadjuvant chemotherapy.

Pietenpol and her team performed high-throughput chemical screens on TNBC cell lines with varying amounts of MYCN expression. They determined that cells with higher MYCN expression were more sensitive to BET inhibitors.

“We have identified MYCN-expressing TNBC cell populations within a substantial fraction of evaluated tumors that have the ability to survive various forms of drug-induced cellular stress, have survival advantages in vitro under selective antiproliferative treatments, and transition between differentiation states (as defined by MYC family expression status),” the study authors reported.

“No the basis of our preclinical results using in vitro and in vivo TNBC models, we posit that BETi and MEKi combination treatment will induce regression of MYCN-expressing TNBC tumors,” they concluded. “Given that patients with TNBC primarily receive systemic cytotoxic chemotherapies that frequently result in unfavorable outcomes, we propose the clinical development of combination BETi and MEKi for patients with advanced TNBC, with parallel evaluation of MYCN as a potential marker for patient selection.”

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—Jennifer Pietenpol, PhD, the Benjamin F. Byrd Jr. Professor of Oncology at Vanderbilt-Ingram Cancer Center

This research opens the door to a promising new approach for certain TNBC patients. “MEK inhibitors have been undergoing drug development, and while it has been challenging with BET inhibitors due to adverse events, there is potential,” Pietenpol noted. “Anytime you can think of new combinations for patients who have diseases with unfavorable outcomes, it really provides a promise of a new opportunity for therapy,” she continued. “And TNBC is a difficult-to-treat cancer with unmet medical need.”

The research team acknowledged that there were limitations to this study. “MYCN-expressing cells exist within highly heterogeneous intratumoral cell populations. Our assessment of MYCN expression in TNBC tumors is limited to the tissue sections under investigation and may not be representative of the entire tumor,” the study authors noted. “Thus, the number of MYCN-expressing TNBC tumors may be higher than reported here.

“We also demonstrate the presence of MYCN-expressing cells in residual disease after neoadjuvant chemotherapy and PI3K inhibitor treatment. Whether MYCN-expressing cells were preexist- ing and selected for with treatment or whether epigenetic events upregulated MYCN expression in cells initially devoid of MYCN remains unclear,” they continued. “Last, the restricted availability of MYCN-expressing TNBC models for in vitro and in vivo preclinical evaluation limits analyses of the effects of combined MEKi and BET inhibitor treatment across a larger cohort of MYCN-expressing TNBC.”

**Ongoing Discovery**

How does this research impact TNBC and future treatment approaches? “The study provides the rationale to advance this combination when we can identify compounds that could be used safely together in humans,” noted Pietenpol, whose hope is to be able to conduct a phase I/IIb clinical trial to test the potential of this combination. The call to action, she emphasized, is the development of BET inhibitors with a good safety profile. “This study highlights an area that requires increased focus because these patients need more effective options.

This research provides preclinical data for investigation of the potential utility of MEKi and BET inhibitors in advanced TNBC,” Pietenpol emphasized. “As a next step, our research team is proposing the further development and clinical trials of this combination therapy.”

Catlin Nalley is a contributing writer.