

differences in eating behaviors nor physical activity according to social connectedness were found. Emotional support from any source was positively associated with sleep quality ($B=0.20$; $SE=0.08$; p -value 0.015). On days when caregivers indicated their spouse appreciated them 'A lot' versus 'Not at all,' sleep quality was marginally better ($B=0.73$, $SE=0.42$; p -value 0.08). Finally, days when caregivers felt lonely at least 'Some of the time' versus 'Not at all' were associated with experiencing more adverse health symptoms ($B=1.54$; $SE=0.58$; p -value <0.001). **DISCUSSION/SIGNIFICANCE OF FINDINGS:** Improved emotional support from any source may support better sleep quality among caregiving spouses, while loneliness appears to contribute to more adverse health symptoms. Findings, if confirmed, can be translated to develop intervention programs that target loneliness and perceived emotional support among caregivers.

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Reversing the resistance to chemotherapy in White and Black patients with triple negative breast cancer (TNBC).

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ABSTRACT IMPACT: Reversing tumor microenvironment (TME) immunosuppression will help to increase the overall efficacy of treatment of chemo-resistant triple negative breast cancer (TNBC) and mitigate racial disparities in treatment response. **OBJECTIVES/GOALS:** We have developed an ex-vivo whole tissue culture model to test the feasibility of reversing local immunosuppression in TME by chemokine modulatory (CKM) regimen. Our current objective is to analyze the molecular changes in CKM-treated chemoresistant TNBC from White and Black women and identify factors determining response to CKM. **METHODS/STUDY POPULATION:** Freshly resected residual TNBC from 20 White and 20 Black women ≥ 18 yrs old treated with neoadjuvant chemotherapy (NAC) will be procured. Tumor explants will be prepared & cultured in the absence and presence of CKM (Interferon- δ $\geq 1/4$, TLR3 agonist rintatolimod and COX-2 inhibitor celecoxib). Chemokines implicated in cytotoxic T-lymphocyte (CTL)- & MDSC/ Treg attraction will be analyzed using Taqman & ELISA. We will have 80% power to detect a 0.7 standard deviation difference in chemokines between untreated & treated samples within and between cohorts using ANCOVA. Bulk RNA sequencing will be performed on both untreated & treated samples from CKM responding (highest aggregate increase in CTL and highest decrease in Treg/MDSC-favoring chemokines in the top quartile) and non-responding (bottom quartile) tissues. **RESULTS/ANTICIPATED RESULTS:** Our preliminary data show that Black patients (pts) with breast cancer (BC) have an immunosuppressive TME associated with poor outcomes. This is similar to other existing literature showing that Black pts with BC have less favorable and more unfavorable chemokines in the TME. We anticipate the chemokine changes with CKM treatment will be larger in the Black cohort given their ability to elicit a robust inflammatory response. Therefore, we expect that CKM treatment will result in favorable TME in both groups and improve outcomes in TNBC, which has the worst prognosis of all subtypes, eliminating a key area of disparity in BC. The proposed transcriptome analysis will help identify key gene networks involved in response to CKM treatment and guide modulating the targets for non-responsiveness to improve efficacy of CKM. **DISCUSSION/SIGNIFICANCE OF FINDINGS:** Pts with

residual disease (RD) after NAC have a 3-yr overall survival 68% vs. 94% for pts with complete response. Blacks have a higher incidence of TNBC with more likelihood of RD & mortality. We anticipate that the existing TME differences can be abrogated by our current CKM regimen or via developing an alternative CKM regimen optimized for Black pts.

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Dual activation of CAR and Nrf2 improves the efficacy: toxicity ratio of cyclophosphamide and doxorubicin-based treatment of TNBC

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ABSTRACT IMPACT: Triple negative breast cancer (TNBC) affects 10-20% of women with breast cancer and is biologically more aggressive than other subtypes. The novel compound we have developed, DL7076, would give clinicians a vital strategy to improve the commonly used cyclophosphamide (CPA) and doxorubicin (DOX) regimen in the treatment of TNBC. **OBJECTIVES/GOALS:** The objective of this research project is to develop a novel compound which can activate both 1) the constitutive androstane receptor (CAR) and subsequently enhance the CYP2B6-mediated activation of CPA, and 2) the nuclear factor erythroid-related factor-2 (Nrf2) leading to the cardiomyocyte protection from DOX-associated cardiotoxicity. **METHODS/STUDY POPULATION:** Following the identification of the compound candidate, DL7076 was evaluated for tissue specific induction of CAR and Nrf2 using qPCR, western blot analysis, and luciferase reporter assays.

Further, we have developed a multicellular coculture model incorporating human primary hepatocytes for metabolism, TNBC spheroids as the target, and cardiomyocytes as a side target of DOX. We have investigated the anticancer effects of CPA/DOX on TNBC cells and the toxic effects on cardiomyocytes with/without a CAR-Nrf2 activator, in a multicellular environment where hepatic metabolism is well-retained. **RESULTS/ANTICIPATED RESULTS:** We found that our dual activator of CAR and Nrf2, DL7076, exhibits tissue specific induction of CAR and Nrf2. Inclusion of DL7076 in combination with the CPA/DOX regimen improves anticancer efficacy, through the subsequent increase in the formation of the active CPA metabolite. With the addition of DL7076, DOX-mediated off-target cardiotoxicity was markedly reduced.

Lastly, utilizing the novel coculture system with human primary hepatocytes, TNBC spheroids, and cardiomyocytes, the inclusion of DL7076 to the CPA/DOX regimen shows decreased spheroid viability and improved cardiomyocyte viability and function. **DISCUSSION/SIGNIFICANCE OF FINDINGS:** Our findings suggest that DL7076 can facilitate DOX/CPA containing regimens by increasing CAR-mediated metabolism and subsequent CPA bioactivation while selectively protecting cardiomyocytes from DOX-induced toxicity. This research is expected to translate our basic scientific findings into therapeutic interventions for women with TNBC.