Weill Cornell Medicine

Enhancing Performance of Checkpoint Inhibitors in TNBC through Copper Depletion

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Background & Unmet Need

- Triple Negative Breast Cancer (TNBC) is a particularly aggressive cancer with poor prognosis, which lacks effective broad-based therapies
- Over 90% of breast cancer deaths are due to metastases, which primarily occur due to resistance to chemotherapy and immunotherapy
- Copper is crucial in tumor progression and metastasis, and supports multiple TNBC resistance pathways in the tumor microenvironment, including:
  - Lysyl oxidase-mediated stromal remodeling, which stiffens collagen and impedes T cell infiltration
  - Enrichment of oxidative phosphorylation
  - Enrichment of highly metastatic cells within primary tumors that initiate metastasis
- **Unmet Need:** New therapeutic strategies targeting resistance pathways for treatment of TNBC

Technology Overview

- **The Technology:** A therapeutic strategy for TNBC combining copper depletion via Tetrathiomolybdate (TM) with pembrolizumab and chemotherapy
- **PoC Data:** A 75-patient phase II pilot trial in late-stage cancer met its primary endpoints of decreased copper levels and reduction of VEGFR2+ endothelial progenitor cells, which initiate the 'angiogenic switch'
- Among stage II/III and stage IV TNBC patients with no signs of disease after standard treatment, the event-free survival rates after an average follow-up of 6.3 years were 90% and 50%, respectively
- This far surpasses the average survival rate of 11% at 5 years for distant metastatic TNBC patients[1]
- Preclinical studies demonstrate that TM reverses key resistance pathways by decreasing collagen density, increasing immune cell infiltration, and shifting cells towards glycolysis

A phase Ib/II clinical trial assessing this combination strategy in patients with residual TNBC is planned

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Patents:
Provisional Filed

Publications:
Liu et al. *NPJ Breast*. 2021.
Ramchandani et al. *Nat Commun*. 2021.
Chan et al. *Clinical Cancer Res*. 2017.

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[1]Shanbhag et al. *Biochin Biophys Acta Mol Cell Res*. 2022.

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Technology Applications

- TM copper depletion therapy for moderate – high risk TNBC patients
- Target patient populations include:
  - TNBC non-responders to chemotherapy / immunotherapy regimens
  - Treatment resistant TNBC with high risk of metastasis
  - TNBC with residual disease

Technology Advantages

- TM is clinically validated agent with proven safety in placebo-controlled trials for Wilson's disease and advanced cancer
- Oral formulation is bioavailable, pharmacodynamic biomarker (copper depletion) easily quantified via ceruloplasmin in the blood
- Ph2 showed striking 5 yr. survival benefit in stage IV pxts vs.TNBC natural history (50% EFS vs. 11%)

Supporting Data / Figures

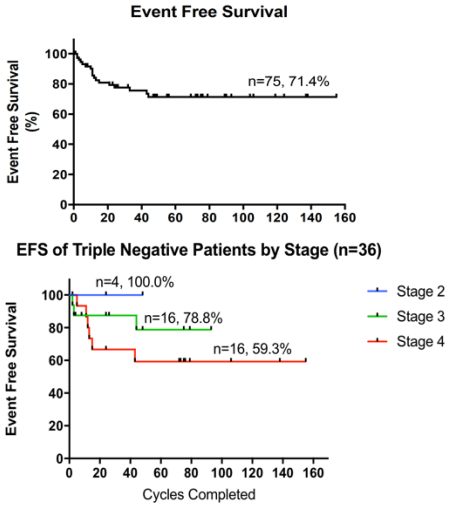

Figure 1: Phase II pilot study of TM (in addition to standard therapy) in advanced cancer patients at moderate-to-high risk of recurrence. At a median follow-up of 10.4 years, the progression-free survival for all 75 patients is 71.4% (top), including a progression-free survival rate of 83% for all stage 2/3 patients with TNBC (bottom). Cycle = 28 days.

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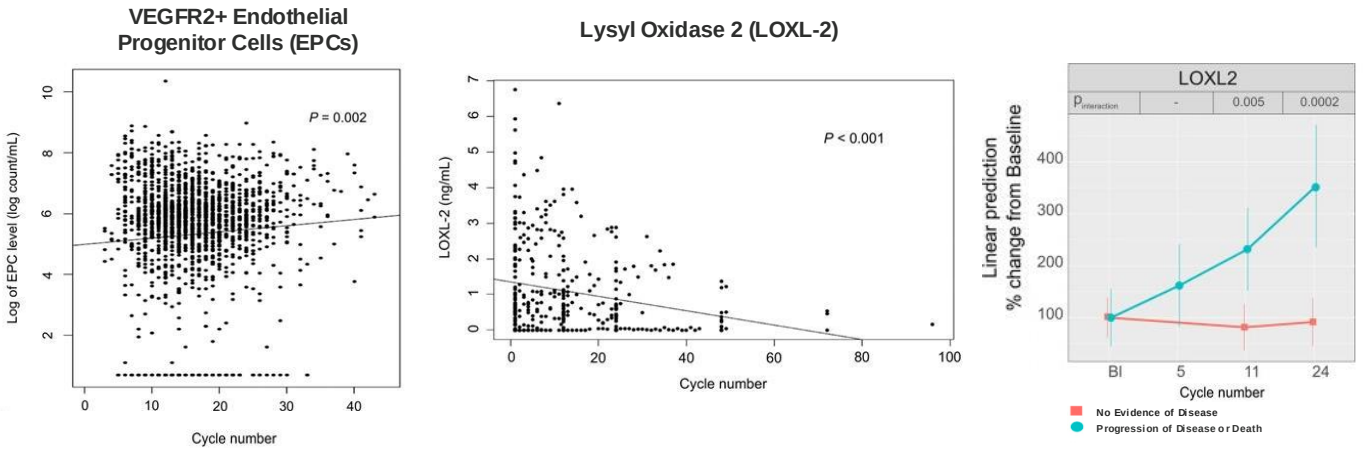

Figure 2: Both VEGFR2+ Endothelial Progenitor Cells (EPCs) and Lysyl Oxidase 2 (LOXL-2) condition the pre-metastatic niche and create a permissive environment for tumor metastases. Data from phase II pilot study of TM in breast cancer patients at moderate to high risk of recurrence demonstrated that VEGFR2+ endothelial progenitor cells (left) and lysyl oxidase 2 (middle) decreased over the course of TM combination treatment. Reduction in LOXL-2 was associated with absence of recurrent disease (right). Cycle = 28 days.

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Collagen Microenvironment | **Immune Cell Infiltration** | **Metabolism**

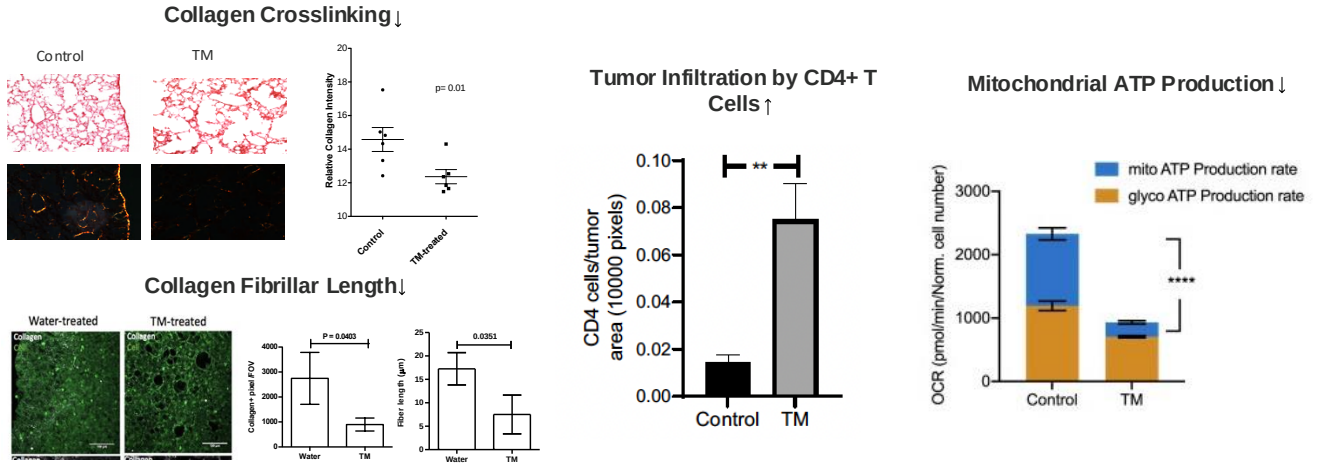

Figure 3: Preclinical studies demonstrate that TM reverses key resistance pathways. TM normalizes the collagen microenvironment (left), increases immune cell infiltration (middle), and shifts tumor cell metabolism away from mitochondrial respiration (right).

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