High-Specificity Theranostic Agent for Triple-Negative Breast Cancer

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Technology description

Triple-Negative Breast Cancer (TNBC) lacks expression of the three common therapeutic targets for breast cancer, which has presented a substantial clinical challenge to the discovery of TNBC-specific targeted therapeutic agents - until now.

The University of Texas at Dallas is seeking companies interested in commercializing the first known TNBC-specific theranostic agent, LC129-8, towards potential applications in TNBC detection and diagnostics, anti-TNBC therapeutics, and as a chemosensitizing agent. The theranostic agent exhibits high-specificity in biological activity toward cancer cells of a particular phenotype: selectively binding TNBC over non-TNBC cells. LC129-8 also exhibits innate anti-TNBC-activity by inducing apoptosis, inhibiting proliferation, reversing epithelial-mesenchymal transition (EMT), downregulating cancer stem cell (CSC) activity, and blocking in vivo tumor growth. Results suggest that prolonged exposure of TNBC tumors to LC129-8 could change the phenotype of TNBC, lowering capability of malignant transformation and attenuating chemotherapy resistance to cisplatin. Moreover, in vivo studies using mouse xenograft indicated that mice treated with the compound didn't show significant tumor growth, suggesting that the compound can efficiently suppress TNBC tumor growth in vivo.

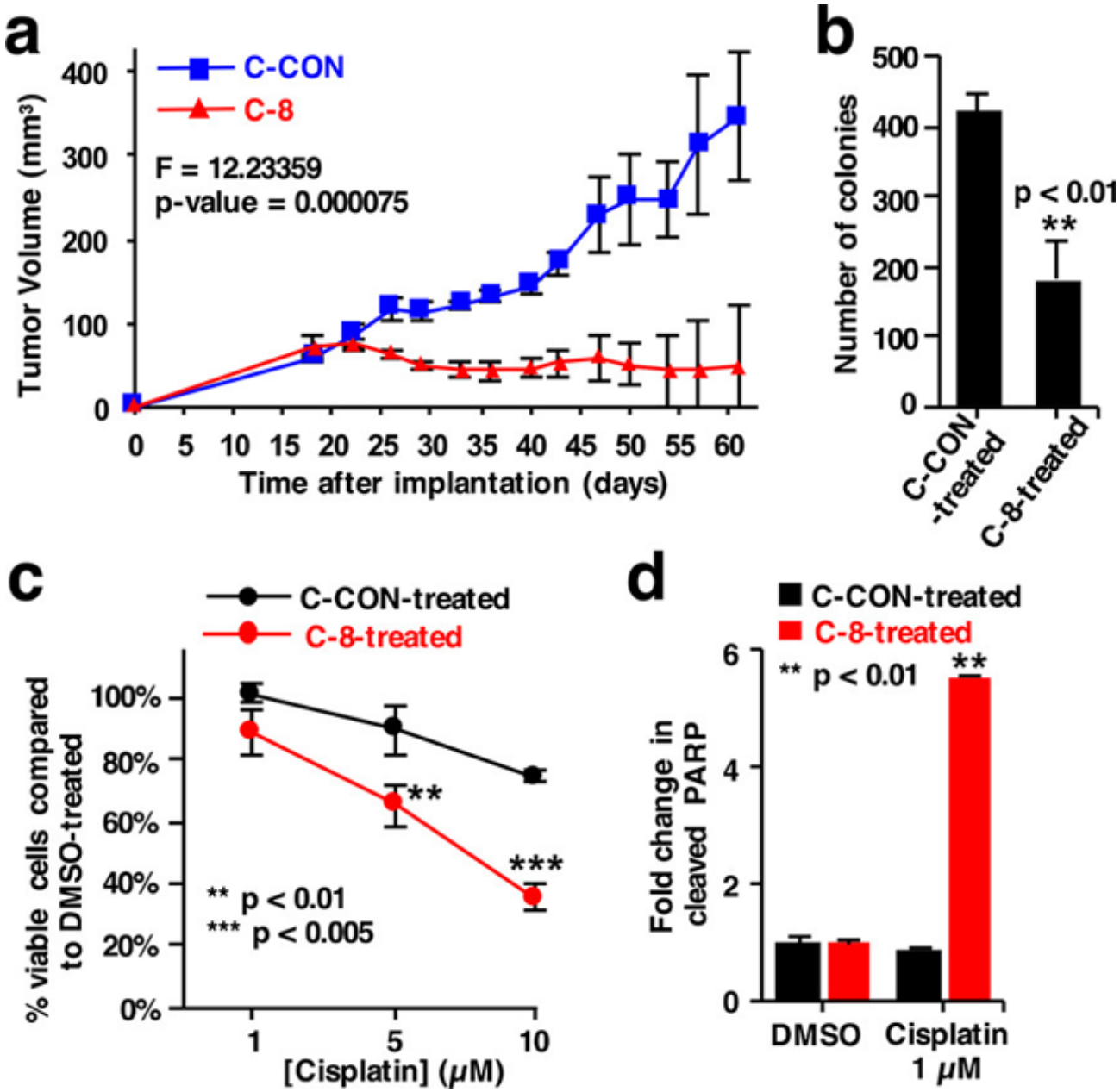

Figure 1: LC129-8 inhibits TNBC tumor growth in vivo and modulates TNBC phenotype.(a) Tumor growth of mice treated with cysteine-conjugated LC129-8 (C-8) or cysteine-conjugated control (C-CON). (b) Quantitation of soft-agar colony formation of the cells extracted from C-8 or C-CON-treated tumors. (c) Cell viability of the C-8 or C-CON-treated tumors cells with increasing doses of cisplatin. (d) WB analysis to evaluate the level of cleaved PARP of C-8 or C-CON-treated tumor cells upon treatment with cisplatin for 24 h.

Technical Summary:

The highly-specific binding of LC129-8 was validated across all TNBC cell lines tested, including patient-derived tumor tissues, and showed that no binding was observed for normal mammary epithelial cells (MCF10A) nor non-TNBC cell lines (MCF-7, T47D, and SKBR3). The compound exhibited TNBC-specific anti-tumor activity in vitro and in vivo, with preliminary studies showing excellent stability in serum. The theranostic agent increased levels of apoptosis-associated caspases and inducing upregulation of pro-apoptotic Bcl-2 family proteins, Bax and Bak, for TNBC cells alone.

As TNBC has been suggested for its higher metastatic potential than other breast cancer subtypes, it is significant that LC129-8 effectively inhibited MDA-MB-231 cell migration in the wound healing assay performed. Moreover, results indicate that this anti-metastatic activity may be contributed to LC129-8 effectively reversing EMT by inducing downregulation of mesenchymal markers and promotion of epithelial phenotypes by preventing the nuclear localization of β-catenin. Cells extracted from LC129-8-treated tumors showed significantly increased sensitivity to cisplatin, providing evidence for the compound's use as a chemotherapy sensitizer.
Value Proposition:
The first TNBC-specific theranostic agent, LC129-8, exhibits anti-TNBC activity by inducing apoptosis, inhibiting proliferation, reversing EMT, downregulating CSC activity, and blocking in vivo tumor growth. LC129-8 has been validated across several cell lines, including patient-derived tumor tissues, and is ready to be developed towards TNBC diagnostics and early-stage targeted therapeutics.
Chen, Luxi, et al. "A Phenotypic Cell-Binding Screen Identifies a Novel Compound Targeting Triple-Negative Breast Cancer." ACS Combinatorial Science, vol. 20, no. 6, 2 May 2018, pp. 330–334., doi: 10.1021/acscombsci.8b00026.

Application area

Diagnostic Test– Could test for TNBC with a single key detection reagent (typical tests require three reagents)
Targeted Cancer Therapeutics– Potential for use as chemotherapy sensitizer, prolonged exposure of TNBC tumors to LC129-8 could attenuate CSC properties
Imaging Agent– In-vitro and in-vivo detection of TNBC enables distinction from non-TNBC cells to assess potential for metastatic carcinoma

Advantages

Stable– Peptoid-based compound is protease-resistant, preliminary study showed excellent stability in serum; Easy to synthesize and store
High-specificity- verified in TNBC cell lines and patient-derived tumor tissue microarray
Anti-TNBC Activity- Induces apoptosis, inhibits proliferation, reverses epithelial-mesenchymal transition, downregulates CSC activity and blocks in-vivo tumor growth

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