A Mouse Model for Triple-Negative Breast Cancer Stem Cells (TNBC-CSC) Exhibits an Aggressive Phenotype

July 28, 2015

Transcriptomics 2015
Orlando, FL

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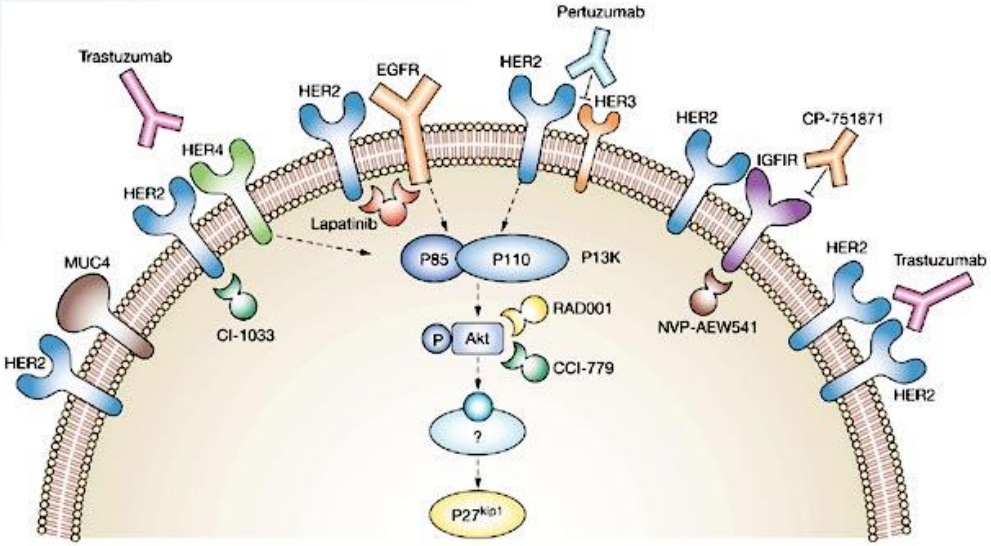
Triple-Negative Breast Cancer (TNBC)

Recent studies on surface receptors and gene expression of breast tumors have come up with a term triple-negative breast cancer (TNBC). 15% of all breast cancers is TNBC and very high in African American (AA) and Hispanic (HP) women.

The disease gets its name because of testing negative for:

Estrogen Receptor (ER)
Progesterone Receptor (PgR)
Human Epidermal Growth Factor Receptor 2 (HER2) gene



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Triple-Negative Breast Cancer (TNBC)

TNBC ($HER2^-/ER^-/PgR^-$) - Creates a disease quite distinct from that seen in CA women ($HER2^+/ER^+/PgR^+$), and is a much more aggressive disease without tumor-specific treatment options.

Although slightly responsive to chemotherapy, TNBC is more difficult to treat and generally insensitive to most available hormonal or targeted therapeutic agents.

Depending on its stage of diagnosis, TNBC can be extremely aggressive-recurring and metastasizing more often than other subtypes of breast cancer.

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Triple-Negative Breast Cancer (TNBC)

Despite lower incidence and the steady improvement in screening, women of African Ancestry (AA) are more likely to die of breast cancer than Caucasian women (CA).

DOI: 10.1093/jnci/djq215
Advance Access publication on June 23, 2010.

ARTICLE

Race and Ethnicity and Breast Cancer Outcomes in an Underinsured Population

Ian K. Komenaka, Maria Elena Martinez, Robert E. Pennington Jr, Chiu-Hsieh Hsu, Susan E. Clare, Patricia A. Thompson, Colleen Murphy, Noelia M. Zork, Robert J. Goulet Jr

Manuscript received August 28, 2009; revised April 26, 2010; accepted M

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American Journal of Epidemiology
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Vol. 162, No. 8
DOI: 10.1093/aje/kwi278
Advance Access publication August 24, 2005

Original Contribution

Risk Factors for Fatal Breast Cancer in African-American Women and White Women in a Large US Prospective Cohort

Marjorie L. McCullough, Heather Spencer Feigelson, W. Ryan Diver, Alpa V. Patel, Michael J. Thun, and Eugenia E. Calle

From the Department of Epidemiology and Surveillance Research, American Cancer Society, Atlanta, GA.

Received for publication March 28, 2005; accepted for publication June 1, 2005.

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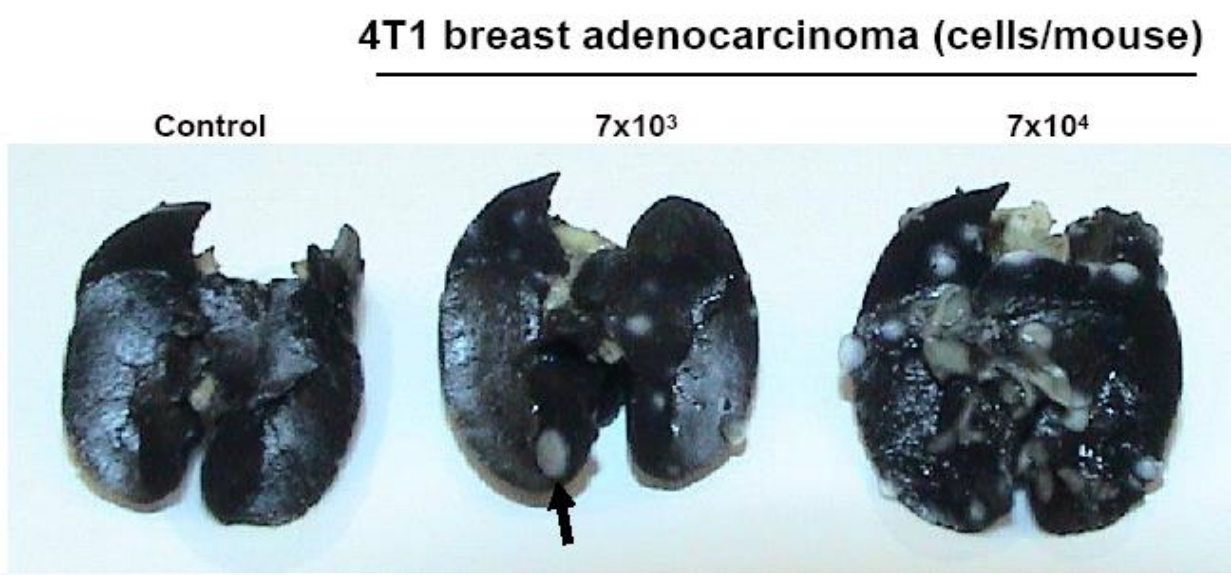
In Vivo Tumor Model



Murine breast carcinoma 4T1 cells are a 6-thioguanine-resistant cell line selected from 410.4 tumor without mutagen treatment. When injected into the abdominal breast gland of female BALB/c mice (8–12 weeks old), 4T1 spontaneously produce highly metastatic tumors that can metastasize to the lung, liver, lymph nodes and brain while the primary tumor is growing in situ. The primary tumor does not have to be removed to induce metastatic growth. The tumor growth and metastatic spread of 4T1 cells in BALB/c mice very closely mimic human breast cancer.

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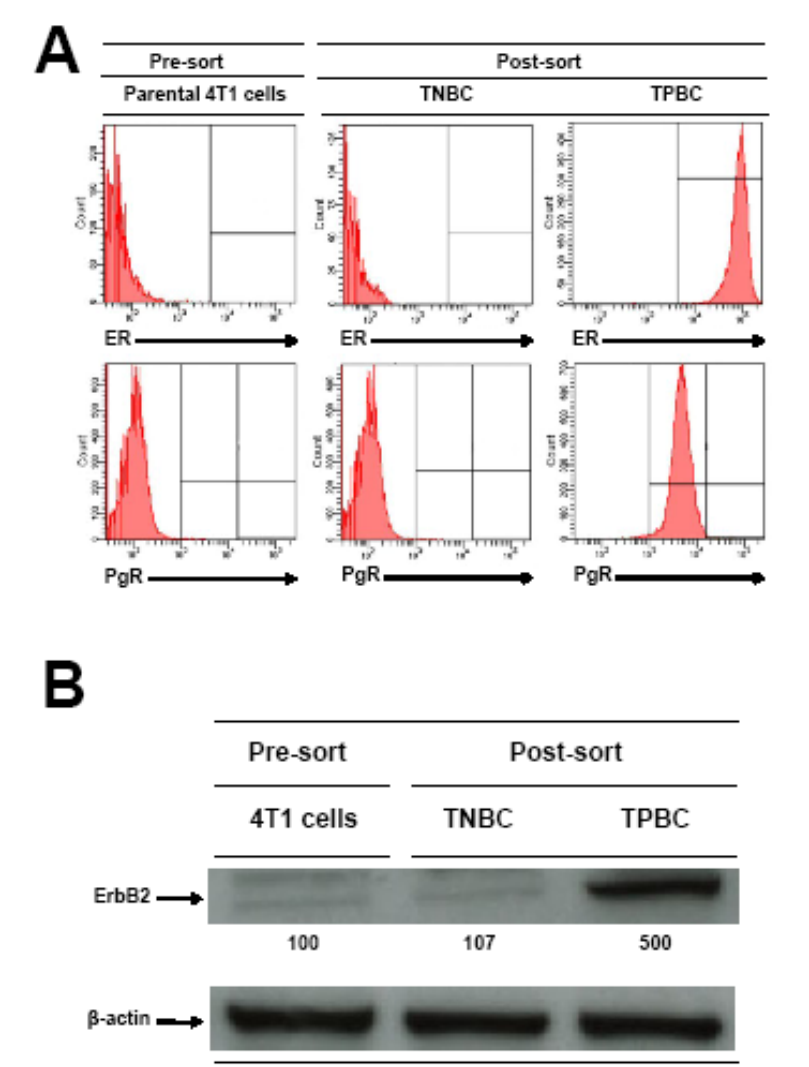
Transfection of rat HER2, ER and PgR genes into 4T1 cells produces a population of TNBC and TPBC



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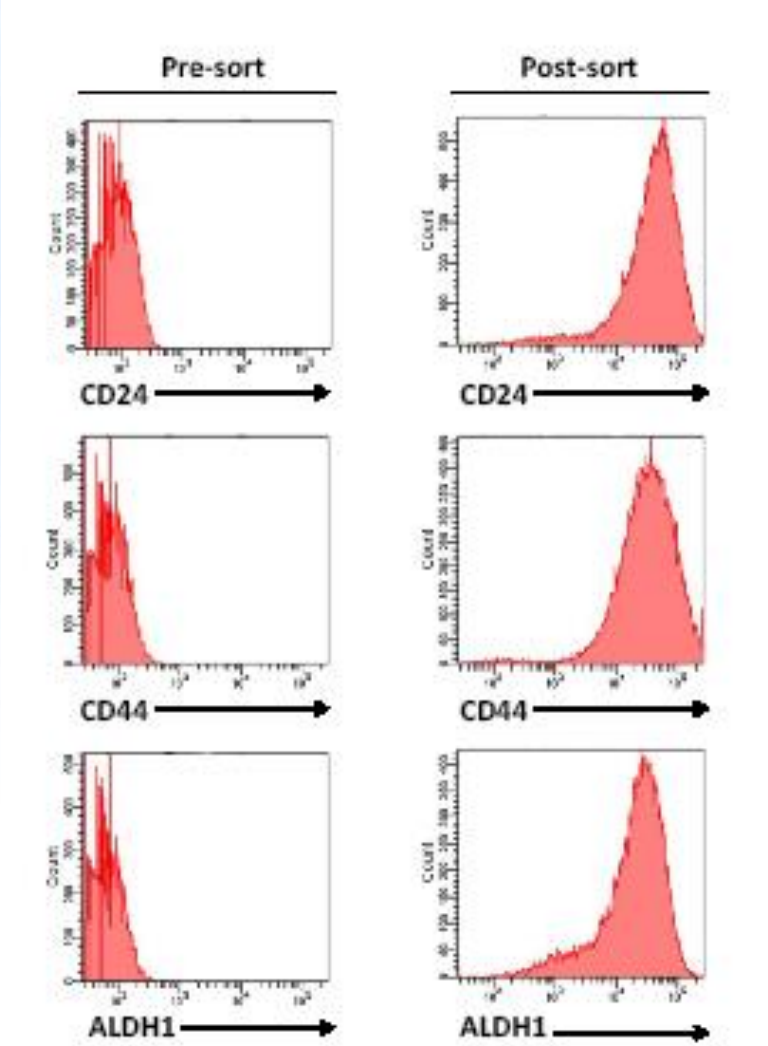
Selection of triple-negative breast cancer-cancer stem cells (TNBC-CSC) as a Tumor Initiating Cells (TIC)



TNBC-TICs exhibit a greater clonogenic growth potential as compared to TNBC, TPBC-TICs, TPBC or parental 4T1 cells

Table 1. TNBC-TICs exhibit a greater clonogenic growth potential as compared to TNBC, TPBC-TICs, TPBC or parental 4T1 cells.

Cell type[1]	Number of cells transplanted	Fraction of mice with tumors[2]
TPBC-derived:		
$CD24^+/ALDH1^+/CD44^{high}$	500	5/5
$CD24^+/ALDH1^+/CD44^{high}$	100	5/5
$CD24^+/ALDH1^+/CD44^{high}$	50	4/5
$CD24^+/ALDH1^+/CD44^{high}$	25	2/5
$CD24^+/ALDH1^+/CD44^{high}$	10	3/5
TPBC-derived:		
$CD24^+/ALDH1^-/CD44^{low}$	500	1/5
$CD24^+/ALDH1^-/CD44^{low}$	100	0/5
$CD24^+/ALDH1^-/CD44^{low}$	50	0/5
$CD24^+/ALDH1^-/CD44^{low}$	25	0/5
$CD24^+/ALDH1^-/CD44^{low}$	10	0/5
TNBC-derived:		
$CD24^+/ALDH1^+/CD44^{high}$	500	5/5
$CD24^+/ALDH1^+/CD44^{high}$	100	5/5
$CD24^+/ALDH1^+/CD44^{high}$	50	5/5
$CD24^+/ALDH1^+/CD44^{high}$	25	5/5
$CD24^+/ALDH1^+/CD44^{high}$	10	4/5
TNBC-derived:		
$CD24^+/ALDH1^-/CD44^{low}$	500	1/5
$CD24^+/ALDH1^-/CD44^{low}$	100	0/5
$CD24^+/ALDH1^-/CD44^{low}$	50	0/5
$CD24^+/ALDH1^-/CD44^{low}$	25	0/5
$CD24^+/ALDH1^-/CD44^{low}$	10	0/5

[1]Tumor cells derived from TPBC or TNBC cells were stably transfected with eGFP using the lentivirus transduction technique as described in detail in the Methods section.

[2]Twenty-one days post tumor cell transplantation into the mammary pad of naïve female BALB/c mice, animals were scarified and eGFP signal from the tumors were measured using the Maestro™ *in vivo* imaging system (CRI), and spectral unmixing was performed to segregate skin and hair auto fluorescence and to measure the true eGFP signal, as described in detail in the Methods section. Data is the fraction of mice with tumors (n=5).

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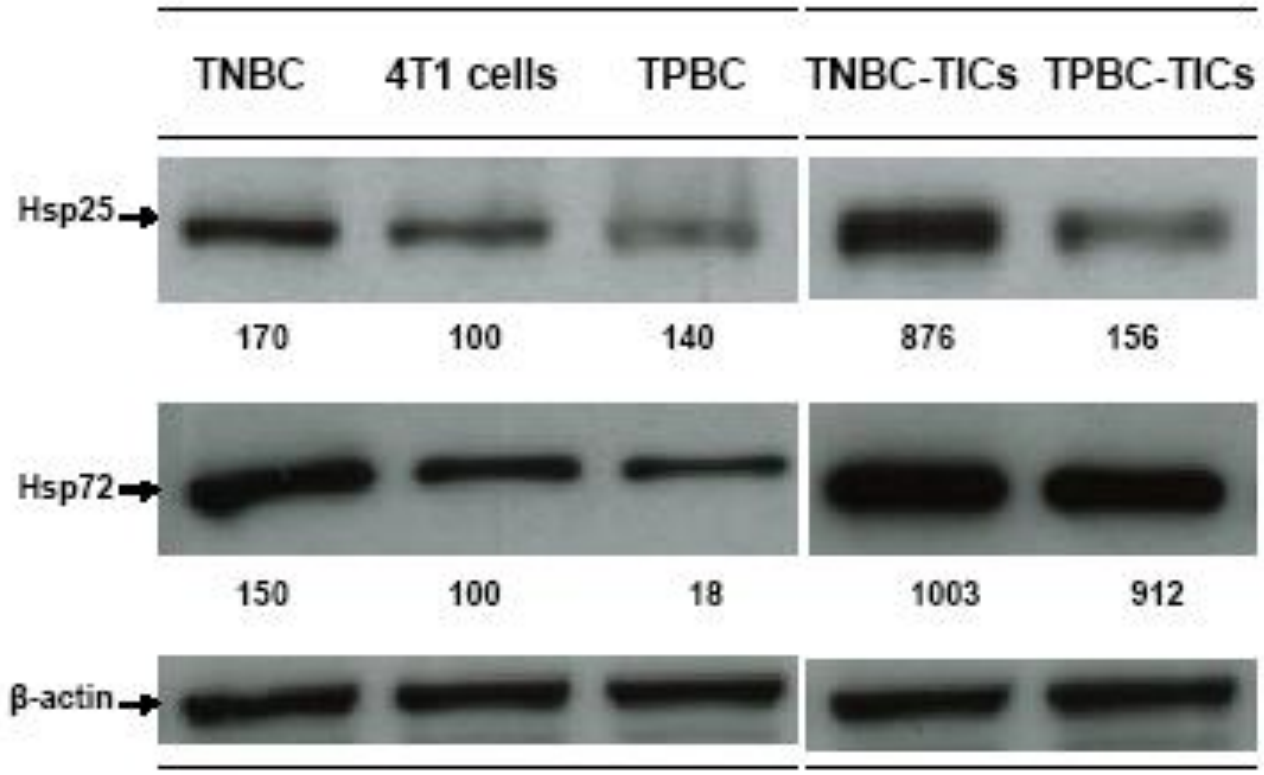
TNBC-TICs express higher levels of Hsp25 and Hsp72/HspA1A than TNBC, TPBC-TICs, TPBC or parental 4T1 cells



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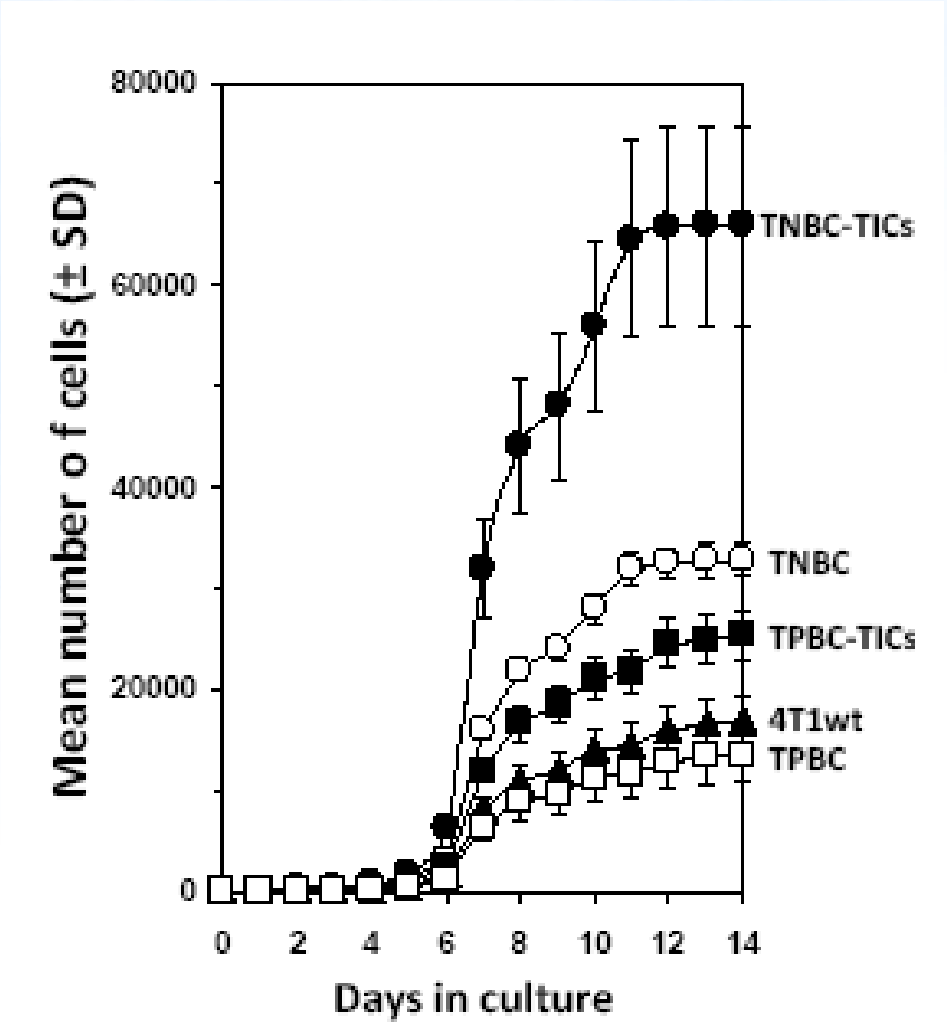
TNBC-TICs proliferate significantly faster than TNBC, TPBC-TICs, TPBC or parental 4T1 cells



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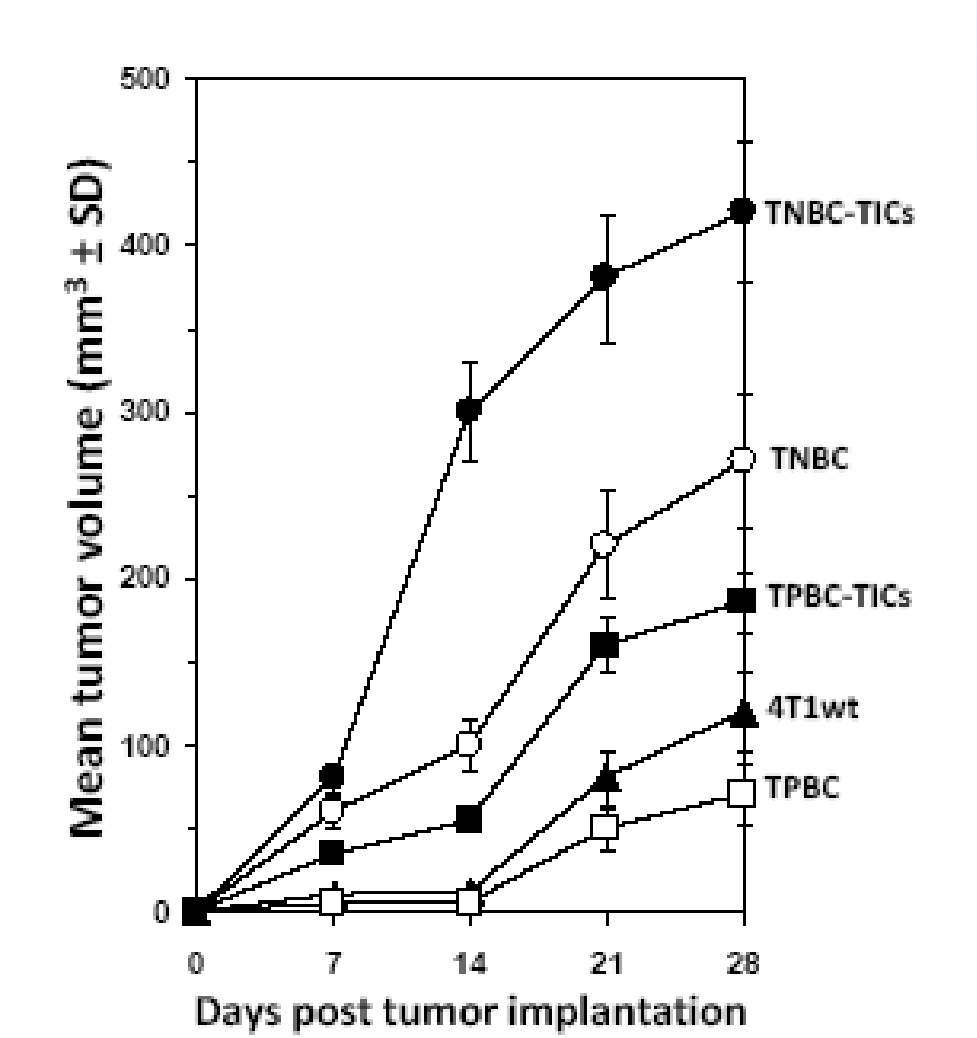
Tumors from TNBC-TICs grow significantly larger than TNBC, TPBC-TICs, TPBC or parental 4T1 cells



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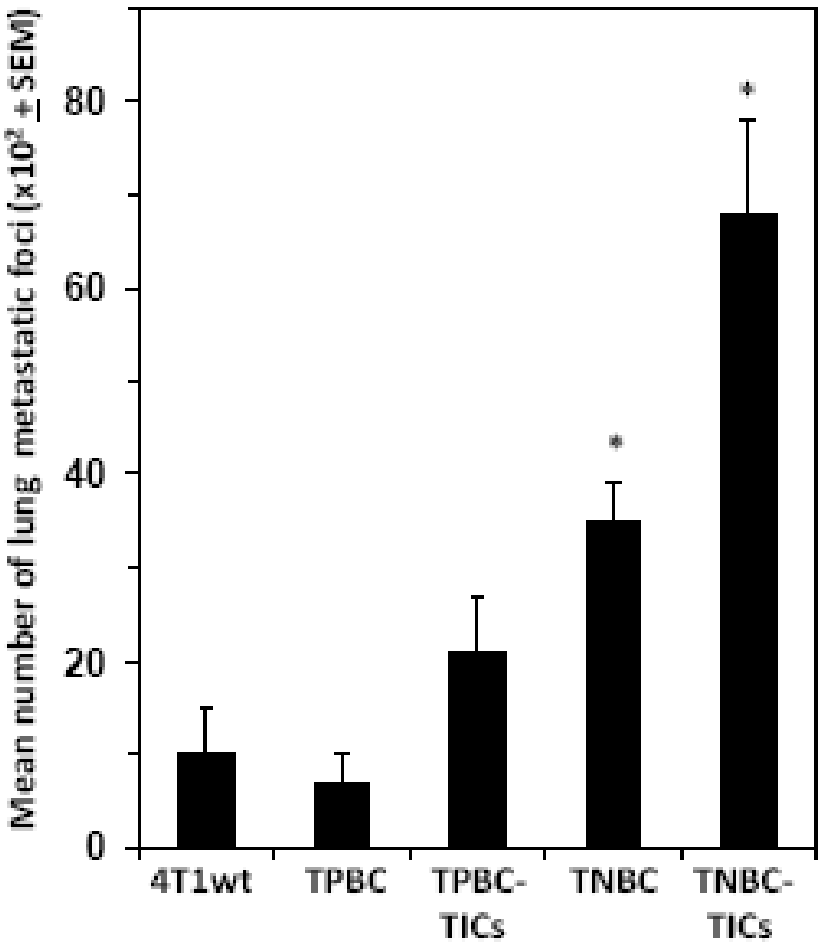
TNBC-TICs produce significantly more metastatic foci than TNBC, TPBC-TICs, TPBC or parental 4T1 cells



Acknowledgements

Dr. Kaur's Lab

This work was funded in part by institutional support from Morehouse School of Medicine and U54 CA118638

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University of Palermo, Italy and University of Dammam, Saudi Arabia