ULTRA HIGH AFFINITY ANTIBODIES ACTIVATE T-CELLS TO TARGET & CONSUME VASCULATURE OF BREAST CANCER MASS

Rice SW, The Golden Zebra Breast Cancer Foundation, Jacksonville, FL 32217
Marks JD, University California San Francisco (UCSF) School Medicine, San Francisco, California 94110
Yee C, University Texas (UT) MD Anderson Cancer Center, Houston, Texas 77054
Thorpe PE, UT Southwestern Medical School, In Memoriam, Dallas, Texas 75390
Brekken R, UT Southwestern Medical Center, Dallas, Texas 75390

ULTRA HIGH AFFINITY ANTIBODIES ACTIVATE T-CELLS TO TARGET & CONSUME VASCULATURE OF BREAST CANCER MASS

(a) Introduction: This project involves **ultra-high affinity (UHA) antibodies** (NEJM 1996;335: 730-33) **enhanced to lock on their target located on the vasculature (blood supply) of breast cancer cell masses**. The patient's own specialized T-Cells (T lymphocytes) can potentially become activated and attracted to the vasculature, bringIng about central necrosis of the malignant tumor without alternate pathway angiogenesis. Funding to be in part from the planned Launch the Cure! concert tour beginning in Madison Square Garden.

(b) Description: Utilizing an immunologic technique designed at UCSF, Marks and others engineered UHA **antibodies having 1,200 times the affinity** towards the HER2-positive breast cancer protein relative to standard monoclonal antibodies. UHA antibodies can potentially recruit and activate human T-Cells to target the vasculature of breast cancers. While results of Herceptin® are known, **targeting the vasculature of a breast cancer mass to bring extremely activated T-Cells to the site, utilizing bi-specific UHA antibodies, has not been described to our knowledge**. T-Cells drawn from individual cancer patients will be expanded in culture, utilizing the technique developed by Yee and others.
T-Cells can be expanded ex vivo to a larger culture of 5 billion T-Cells. The several billion T-Cells will then become Activated ex vivo by an immunogenic breast (and melanoma) cancer cell protein called NY-ESO-1 (NewYork-ESOphageal-1). That New York Activator (renamed for this study NYACT) was identified by an international group of scientists. The extremely activated T-Cells will wear transplanted UHA receptors and will be re-infused into the patient. **The several billion Super T-Cells will then theoretically target and consume the blood supply of breast cancer masses**. The **initial results** of a similar solid tumor research protocol, pioneered by Yee and others, performed **in just one patient with widely metastatic** melanoma, **showed no evidence of disease by CT and PET scans performed at 2 months and again at 22 months, after T-Cell re-infusion**. At long term follow up, the patient had a Karnofsky performance status of 90-100%. **Only a few minor side effects occurred, which resolved within 3 days** (NEJM 2008;358: 2698-703).

(c) **Summary**: The above immunologic technique will potentially allow UHA **antibodies to permeate into and throughout breast cancer cell masses**. The UHA antibodies will theoretically recruit and activate highly specialized T Cells that wear unique ex vivo engineered receptors. This project is **designed to enhance a patient's own immune system to target and consume the central blood supply of breast cancer masses, without significant side effects**.

(d) **Conclusion**: The above immunologic approach to breast cancer is designed to produce necrosis of the vasculature of malignant breast tumors. **The design utilizes ultra-high affinity antibodies and the patient's own immune system to "consume the cancer from within™."**

We have been invited to perform this breast cancer research at the Space Life Science Laboratory near the Kennedy Space Station as part of the N.A.S.A. Mission to Planet Earth.

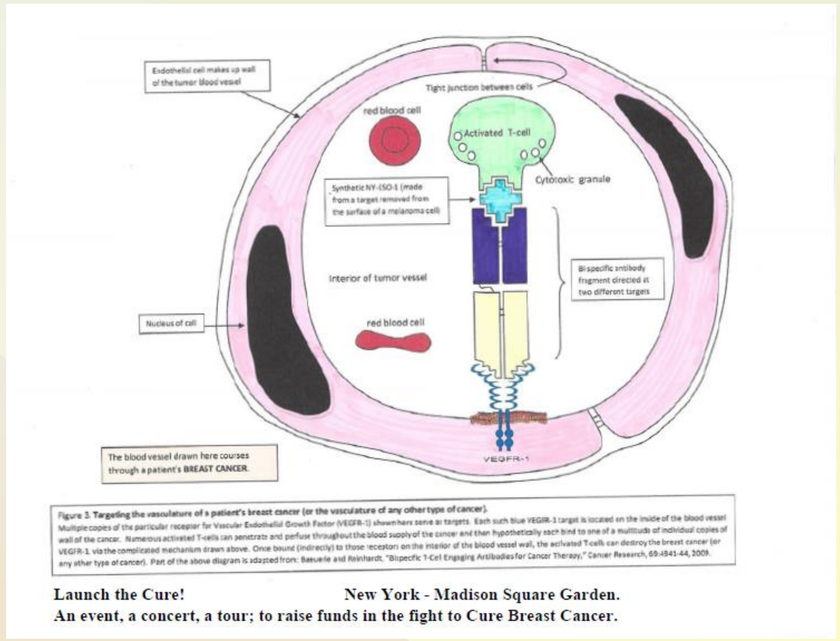
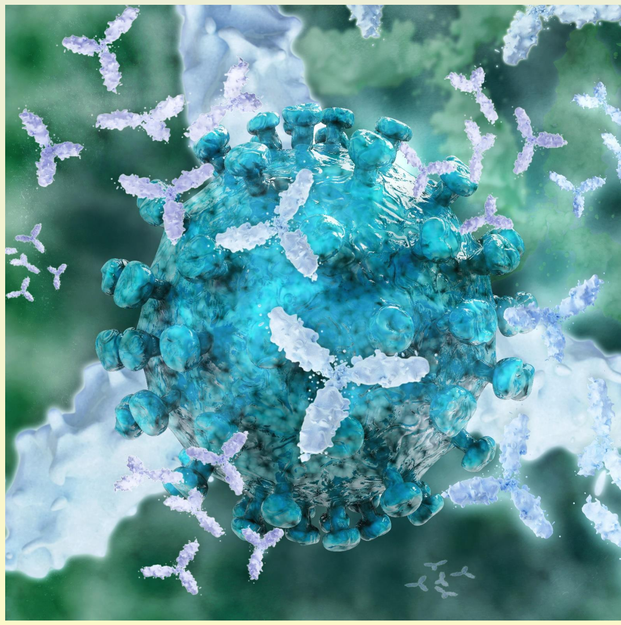


Figure 1. **Targeting the vasculature of a patient's breast cancer.**
Multiple copies of a receptor for Vascular Endothelial Growth Factor (VEGFR-1) shown here serve as targets. Each such lower blue VEGFR-1 or preferably VEGFR-2 target is located on the inside of the blood vessel wall of the cancer. Numerous extremely activated T-cells can potentially penetrate and perfuse throughout the blood supply of the cancer and then hypothetically each bind to one of a multitude of individual copies of VEGFR-1, via the complicated mechanism drawn above. Once bound (indirectly) to those receptors on the interior of the blood vessel wall, the activated T-cells can potentially consume and destroy the breast cancer (or any other type of cancer). Part of the above diagram is adapted from: Baeuerie and Reinhardt, "Bispecific T-Cell Engaging Antibodies for Cancer Therapy." Cancer Research, 69:4941-44,2009

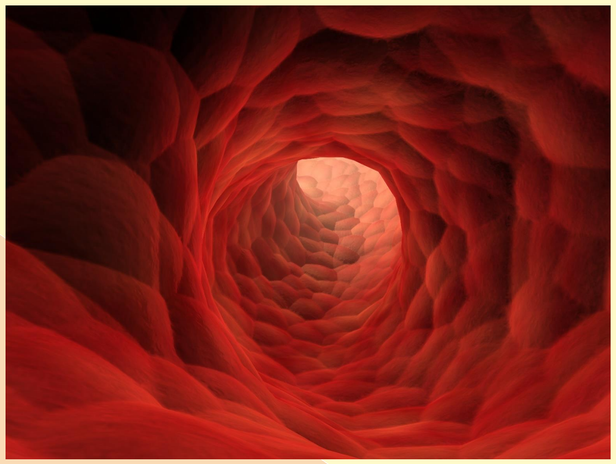
REFERENCES

1) Cara and James D. Marks, "Phage Libraries – A New Route to Clinically Useful Antibodies," NEJM, September 5, 1996, 730-733
2) Naomi Hunder, et al, "Treatment of Metastatic Melanoma with Autologous CD4+ T-Cells against NY-ESO-1," NEJM June 19, 2008; 358:2698-703.
3) Shier, et al, "Isolation of Picomolar Affinity Anti-c-erbB-2 Single Chain Fv by Molecular Evolution of the Complementarity Determining Regions in the Center of the Antibody Binding Site, J. Mol. Biol., 1996, 551-567.
4) Thorpe, et al, "Targeting the Vasculature of Solid Tumours", Journal of Controlled Release, October 13, 1997, Volume 48: pages 277-288.
5) Brekken RA, Thorpe PE, "Vascular Endothelial Growth Factor and Targeting of Solid Tumors. Anticancer Res. 2001, Nov-Dec: 21(6B): 4221-9

We Love Our Mommies



Bi-Specific Ultra High Affinity (UHA) Antibodies with over 1,200 times the affinity of standard antibodies will be utilized to allow extremely activated T Cells to target the vasculature (blood supply) of breast cancer masses.



Launch the Cure!
Scott W. Rice, MD
scott@TheGoldenZebra.Org
7004 San Sabastian Ave
Jacksonville, Florida 32217
www.TheGoldenZebra.Org