Breast Cancer Detection using an engineered B7-H3 affibody ligand

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Technology description

Breast cancer is a lethal disease and patient survival depends on early detection of the disease. Breast cancer is the second leading cause of cancer-related deaths in women in the United States. If detected early, the survival of women with breast cancer can be substantially increased compared to detection at later stages. The 5-year survival rate in patients diagnosed with stage I and II disease is 100% and 98.5% compared to 84.6% and 25.0%, respectively, when detected at stage III and IV disease. Next to breast self-exam and clinical breast exam, the American Cancer Society recommends mammography as a screening exam in women age 40 and older. For high risk women, mammography is recommended at age 30 years. In patients with dense breast tissue, diagnostic accuracy of mammography is severely limited. The presence of dense or heterogeneously dense breast tissue, prevalent in ~50% of patients screened by mammography, particularly in younger patients, may decrease diagnostic accuracy of mammography in detecting breast cancer, with sensitivities ranging between 30% and 55%. At the same time, the rate of overdiagnosis by mammography has been estimated to be 22-31% percent of all breast cancers diagnosed in the United States resulting in a national cost of $4 billion each year. Ultrasound (US) complements mammography as an imaging modality for breast cancer detection, especially in patients with dense breast tissue, but its utility is limited by low diagnostic accuracy. One emerging molecular imaging tool to address this limitation involves contrast-enhanced ultrasound (CEUS) using microbubbles (MBs) targeted to molecular signatures on tumor neovasculature. Stanford researchers have demonstrated how tumor vascular expression of B7-H3 (CD276), a member of the B7 family of ligands for T-cell coregulatory receptors, can be incorporated into an ultrasound method that can distinguish normal, benign, precursor, and malignant breast pathologies for diagnostic purposes. The published proof-of-concept study shows clearly that B7-H3 immunostaining on blood vessels distinguished benign/precursors from malignant lesions with high diagnostic accuracy in human specimens (AUC up to 0.96). In addtion, in a transgenic mouse model of cancer using , the B7-H3–targeted ultrasound imaging signal was increased significantly in breast cancer tissues and highly correlated with ex vivo expression levels of B7-H3 on quantitative immunofluorescence. However, the use of a streptavidin coated MB and a biotin conjugated anti-mouse B7-H3 antibody is not clinically translatable. Therefore, the purpose of this study was to engineer a B7-H3 10 affibody ligand for the use of developing B7-H3-targeted ultrasound contrast agent to detect early stage of breast cancer and to distinguish benign/precursors from malignant lesions with high diagnostic accuracy.

Mammography is the current first-line imaging technique for early breast cancer detection, however, its diagnostic accuracy is limited in women with dense breast tissue. Ultrasound is often performed as a second line test in women with dense breast tissue. However, due to its low specificity, it results in many false positive findings with unnecessary biopsies and increased associated health care costs. Researchers at Stanford and the University of Minnesota have recently identified and validated a novel, highly specific neoangiogenesis marker in patients with breast cancer with high diagnostic accuracy (AUC of up to 0.96).

Application area

Diagnostic imaging of breast cancer.

Advantages

Improvement of the diagnostic accuracy of ultrasound screening exams in detection and characterization of breast lesions in women with dense breast tissue. A theranostic approach to increase therapeutic efficacy.

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