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Receptor internalization facilitates PET imaging of HER3 receptor expression in a preclinical BrCa model

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Introduction: In some HER2+ breast cancer (BrCa), HER3 mediated resistance may be responsible for decreased effectivity of HER2 inhibitors in a high percentage of patients (1, 2). The evaluation of tumor HER3 expression levels may therefore be helpful to stratify patients, which are most likely to benefit from the addition of HER3 inhibitor therapies, which are currently in development (3). PET imaging is hindered by the low copy number of HER3 receptors.

Materials and Methods: In this pilot study we developed and tested a ^{64}Cu-HER3-F(ab')2 PET probe in a mouse model and correlated it with *in vitro* findings determining levels of receptor expression and furthermore depicting presumable HER3 receptor internalization which possibly allows detection of a sufficient PET signal. Anti-HER3-F(ab`)2 was generated from a monoclonal antibody by enzymatic digestion and conjugated with DOTA and labeled with ^{64}Cu. Binding of HER3 to BrCa cells was analyzed by confocal microscopy and internalization studies were analyzed *in vitro*.

Two different human BrCa lines (MCF-7 and MDA-MB-231) were used for in vivo experiments to generate positive and negative tumor models, respectively.

Results: We demonstrated that DOTA-HER3-F(ab')2 exhibited high affinity (Kd: 8,9 ± 0.4 nM) to HER3. There were significant differences of HER3 receptor expression levels across the two different cell lines *in vitro* and in vivo by visual and quantitative assessment methods. Internalization experiments on MCF-7 cells showed significantly higher values (1.89±0.24 (at 37^{0}C) vs. 0.56±0.16 (at 4^{0}C), n=4; p: 0.004) (given as counts/cell±SEM, two-tailed t-test), which could demonstrate the internalization of ^{64}Cu-HER3-F(ab')2 by receptor-mediated endocytosis at 37^{0}C. PET/CT images showed higher tracer uptake in MCF-7 tumors compared to MDA-MB-231 tumors, which are in good correlation with uptake and FACS analysis.

Conclusion: Our experiments suggest that the mechanism of receptor internalization facilitates PET imaging of HER3 expression in a preclinical tumor model and DOTA-HER3-F(ab')2 has the potential to be used as a tumor imaging agent specific for tumors overexpressing HER3.

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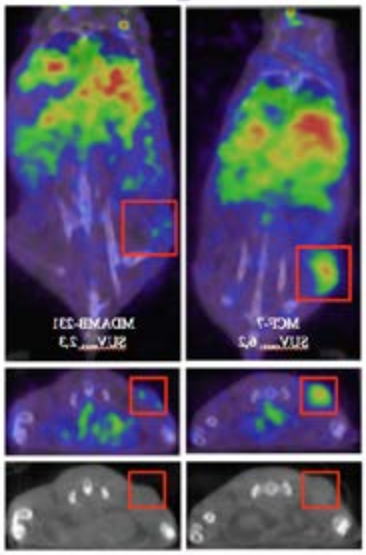

Figure: Small animal PETCT images of female BALB/c mice implanted subcutaneously in right flank with HER3+ and HER3- MCF-7 and MDA-MB-231 human BrCa xenografts 24 h after the injection of ^{64}Cu-HER3-F(ab')2.