Molecular Imaging of Tumor Angiogenesis

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Molecular imaging has evolved dramatically over the last decade and played an important role in cancer diagnosis and patient management. Angiogenesis, the formation of new blood vessels, is one of the hallmarks of cancer. Tremendous effort has been devoted to targeting angiogenesis-related markers, including integrin $\alpha_v\beta_3$, VEGFRs and CD105/endoglin. This dissertation describes the design, synthesis and evaluation of molecular imaging agents for imaging of CD105 and VEGFRs expressions. The applications of these agents in other angiogenesis-related disease models are also discussed.

CD105 is only expressed on proliferating endothelial cells, which makes it an optimal biomarker for targeting tumor angiogenesis. TRC105, a human/murine chimeric monoclonal antibody that binds CD105, was labeled with ^{64}Cu, to yield two PET agents: ^{64}Cu-DOTA-TRC105 and ^{64}Cu-NOTA-TRC105. PET imaging study of CD105 expression with the agents was carried out in a murine tumor model. The specificity of the agents was confirmed by different control experiments. It was demonstrated that NOTA is superior for in vivo application than DOTA. NIRF imaging of CD105 expression is also achieved with NIR dye 800CW labeled TRC105.

One limitation of imaging agents based on intact antibodies is the prolonged circulation half-life. Typically, tumor uptake does not reach the peak until a few days after tracer injection. PET imaging of CD105 expression with antibody fragments will be evaluated and discussed. A more desirable PET isotope ^{61}Cu, with suitable physical half-life and higher positron branch ratio, was employed as the radiolabel.

Multimodality imaging agents targeting CD105 are developed and evaluated in subcutaneous tumor and experimental breast cancer lung metastasis model. TRC105 was labeled with 800CW and either ^{64}Cu or ^{89}Zr, to yield ^{64}Cu-NOTA-TRC105-800CW and ^{89}Zr-Df-TRC105-800CW. The specificity of the two agents was demonstrated in two tumor models and confirmed by control experiments. The potential application of the agents in image-guided surgery was demonstrated.

Non-invasive PET or multimodality imaging of VEGF/VEGFR signaling pathway was achieved using ^{61}Cu labeled $VEGF_{121}$ and dual-labeled bevacizumab, an anti-VEGF mAb. The use of ^{64}Cu-NOTA-TRC105 for PET imaging of CD105 expression in a murine hindlimb ischemia model was also discussed.