Exploiting FcRn-mediated Antibody Internalization for Targeted Imaging and Directed Therapy of Androgen Receptor Controlled Secreted Enzymes

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Background –
Understanding the mechanisms of this resistance in prostate cancer is confounded by a lack of non-invasive means to assess the down-stream androgen-receptor (AR) activity in vivo. Here, we exploit the neonatal Fc-receptor (FcRn) mediated immunological mechanism that allows cells to internalize antibodies that have formed complexes with antigens. We applied this immunobiological mechanism for in vivo targeting of hK2; an AR-governed and prostate specific antigen. Specifically, we investigated the applicability of humanized high affinity hK2-antibody (hu11B6) to guide and deliver therapy, and to monitor response in advanced and novel models of prostate cancer that recapitulate critical phases of the disease in man.

Methods –
A novel anti-free hK2 antibody, 11B6, was produced and humanized. Zirconium-89 (for immunoPET) and alpha emitting Actinium-225 (for molecular radiotherapy) conjugates were generated using clinical labeling protocols and characterized. Imaging and therapy studies were evaluated in vivo using models of human disease (VCaP, LNCaP and PC3) and in a genetically engineered mouse model (GEMM) of prostate-restricted hK2 expression (Myc *X* hK2). Fluorescently labeled (Cy5.5 and FITC) 11B6 was evaluated in vitro (using validated human PCa cell lines) in order to evaluate cellular interaction using laser scanning confocal microscopy.

Results –
Internalization of the antigen-antibody complex was confirmed by confocal microscopy and the relation to FcRn mechanism was confirmed through a missense mutation of the 11B6 Fc-region. Uptake reflects AR pathway activity (validated by chemical and surgical inhibition) in advanced models of cancer development and treatment. Noninvasive immunoPET imaging provides high contrast quantitative delineation of disease, while targeted alpha emitting therapies significantly inhibit disease progression. Humanized 11B6 has undergone toxicologic tests in non-human primates, with no noted toxicity.

Conclusions –
Fluorescent and radio-conjugates of an anti-free hK2 antibody, hu11B6, are internalized and non-invasively report AR pathway activity in human cells as well as advanced GEMM of disease. The role of neonatal Fc-receptor is still being explored, but paves the way to achieve sustained uptake for imaging and therapy of other secreted antigens. Humanized 11B6 has significant potential to improve patient management in these cancers.

Conflict of Interest –
DLJT, HL and HDU are advisors and shareholders in Diaprost LLC.

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