Comparison of Optical Imaging Approaches in 2D and 3D in Disseminated Raji-luc B-cell Lymphoma

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Introduction:
Optical imaging allows staging and tracking of multiple tumors in disseminated tumor models and to this end, bioluminescence (BLI) imaging has been the most common approach. While BLI is cost effective and quantitative, it requires luciferase-engineered tumor lines, which have the disadvantages of time and uncertainty associated with transfection, as well as potential phenotype change in the engineered line, compared with the parent. Exogenous fluorescence probes preferentially activated by tumors provide a similar efficient optical imaging means to tumor burden tracking in these models, directly in any tumor lines of interest. This method also allows 3D imaging through new tomographic optical imaging technologies. In this work, BLI and activated fluorescent probe imaging were used in a luciferase-expressing Raji-luc human Burkitt’s lymphoma model.

Methods:
Raji-luc lymphoma cells were transfected to express luciferase using a lentiviral vector transfection method. Raji-luc cells were (1e+07) injected IV in CB-17 mice on Day 0. Bioluminescence scans were used to determine the distribution of light throughout the body immediately following implantation. In vivo and ex vivo bioluminescence imaging was used to localize tumor signals and determine incidence and tumor growth. Both cathepsin- (ProSense) and MMP- (MMPSense) activated fluorescent probes were injected IV 24h prior to fluorescence molecular tomographic imaging.

Growth Characteristics
- 100% take rate for C.B-17 and NOD C.B-17 mice based on BLI signal. <45% take rate for SHO mice.
- Doubling time= 2.7 days.
- Median day of death for C.B-17 @1x10⁷ cells= 19 days
- Treated groups= Cyclophosphamide @100mg/kg, IP, QDx5; and Rituximab @ 10mg/kg, IV, Q4Dx3.

Results and Discussion:
Bioluminescence imaging of intravenously injected Raji-luc cells from one to four weeks after inoculation showed a high incidence of tumor growth at sites including hind limbs, spine, and brain in addition to lung and to a lesser extent, the axillary lymph nodes and sternum. Fluorescence tomographic imaging with tumor activated probes provided a measure of disseminated tumor burden, but had the disadvantage of normal tissue background, compared with BLI where there was inherently no normal tissue background. Activated fluorescent probe imaging provides a viable means for imaging in disseminated tumor models without the need for engineered cell lines.

Conclusions
- A new Raji-luc model was established and validated for IV-injection format and response to standards of care.
- Luc-enabling the Raji cell line allowed tracking of focal lesions using BLI.
- FMT imaging using both cathespin and MMP-activated probes allowed detection of Raji-luc tumors and images correlated well with BLI scans.