Picture perfect: alpha imaging confirms efficient targeting

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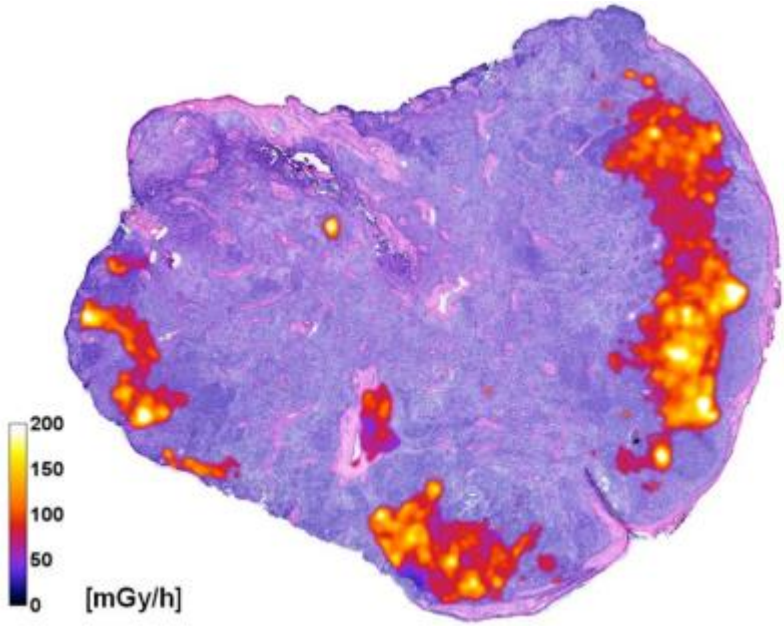

A hematoxylin and eosin (H&E)-stained section of a canine lymph node showing the At-211 dose rate distribution in red/yellow, quantified through alpha imaging. The lymph node was biopsied and immediately frozen two hours after the radioactive injection, at which point the accumulation of At-211 was high in the T cell-rich paracortex.

Image provided by Dr. Tom Bäck

Hematopoietic cell transplantation can successfully cure many hematological diseases including cancers. The success of this therapy depends on efficiently removing malignant cells, as well as suppressing the immune system of the patient. Chemotherapy and whole body gamma irradiation are standard conditioning regimens, yet these aggressive approaches have extensive side effects. Radiolabeled monoclonal antibodies are being explored as approaches to increase the specificity and efficacy for targeting host hematopoietic cells. Monoclonal antibodies (MAbs) targeting the cell surface protein CD45 are known to recognize nearly all hematopoietic cells and serve as an excellent targeting agent; however, to date studies have mainly paired anti-CD45-expressing MAbs with beta-emitting isotopes. Compared to beta emitters, alpha-emitting isotopes release higher-energy particles with shorter range, which is likely to increase both the specificity and the efficacy of the treatment. Dr. Sofia Frost and colleagues from the Clinical Research Division demonstrate the feasibility of alpha-radioimmunotherapy in The *Journal of Nuclear Medicine*.

The high energy and short range of alpha radiation is ideal for antibody-guided targeted therapies of hematological malignancies, however, the limited particle range makes calculation of absorbed radiation doses in tissues difficult. In this study, Dr. Frost and investigators overcame this challenge

using *ex vivo* alpha imaging in a canine model. Anti-CD45-expressing MAbs were radiolabeled with the alpha emitter astatine-211 (^{211}At) and infused into animals. Using alpha imaging and flow cytometry of biopsied bone marrow and lymph node samples the researchers demonstrated that this targeted approach was comparable to current pre-treatment approaches utilizing whole body gamma radiation, " We are showing that the absorbed doses that are achieved in this model compare well with, or exceed, those used in standard external beam total body irradiation regimens" , said Dr. Frost. The high spatial resolution of the alpha images makes this techinque sensitive enough to efficiently reveal the specificity of ^{211}At-conjugated anti-CD45 MAbs. Different regions within lymph nodes contain varying amounts of CD45-positive immune cells, and by alpha imaging these were clearly distinguished. The T cell-rich paracortex, for instance, was the region that contained the most ^{211}At-anti-CD45. Thus the authors conclude that ^{211}At-anti-CD45 radioimmunotherapy efficiently targets hematopoietic cells for transplant pre-treatment without severe toxicity, and that *ex vivo* alpha imaging enables better prediction and understanding of the therapeutic outcome.

These initial safety and biodistribution studies will allow for test treatments of canine patients with spontaneous lymphoma. Excitingly, human applications are also underway, " Clinical trials using alpha emitters like astatine-211 are currently being developed at Fred Hutch…and we anticipate they will open in the next year." said Dr. Frost.

Frost SHL, Miller BW, Bäck TA, Santos EB, Hamlin DK, Knoblaugh SE, Frayo SL, Kenoyer AL, Strorb R, Press OW, Wilbur DS, Pagel JM, Sandmaier BM. 2015. Alpha imaging confirmed efficient targeting of CD45-positive cells after Astatine-211 (^{211}At)-radioimmunotherapy for hematopoietic cell transplantation. J Nucl Med. 56(11):1766-73. doi: 10.2967/jnumed.115.162388.

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