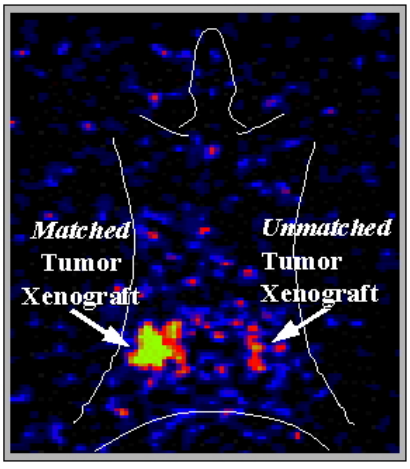
Tumor Targeting and Cell-trafficking Studies of 131I/124I]-FIAU-labeled Genetically Modified Antigen-specific Lymphocytes

Donor T cells are reactive against and effective in adoptive immunotherapy of Epstein-Barr virus (EBV) lymphomas, which develop in some leukemia patients after marrow transplantation. Such T cells have been genetically modified by incorporation of a replication-incompetent vector (NIT) for an inactive mutant nerve growth factor receptor (LNGFR) as an immunoselectable surface marker and a herpes simplex virus thymidine kinase gene (HSV-TK), rendering the cells sensitive to ganciclovir. Current studies are based on the selective HSV-TK-catalyzed phosphorylation and incorporation into DNA of [131I]-2'-fluoro-2'-deoxy-1-b-D-arabinofuransyl-5-iodo-uracil (FIAU) (Tjuvajev et al. *Cancer Res.* 1995;55:6121. / 1996 56:4087.).

In vitro kinetic studies indicate that 131I-FIAU is rapidly (< 1 hour) incorporated into cells. Kinetic measurement of release of radioiodine from the labeled cells and a 51Cr release assay against HLA-matched and HLA-unmatched EBV lymphoma cells demonstrated little loss of cell activity and little reduction of immune cytoxicity or specificity of the genetically modified T cells labeled to absorbed doses of ~2,000 rad — but demonstrated substantial dose-dependent effects thereafter.

In SCID mice bearing EBV lymphoma xenografts matched or unmatched to [131I]-FIAU-labeled donor lymphocytes, gamma camera imaging (see image below) and tissue radioassay post-necropsy indicated remarkably specific localization of the lymphocytes by ~4 days in the matched tumor but much less localization in the mismatched tumor. Matched tumor-to-nontumor (liver, spleen, muscle) activity concentration ratios were ~100:1, with ~1%/gm of the administered activity in the matched tumor.

(This work was performed in collaboration with Drs. Gunther Koehne of the Bone Marrow Transplant Service, Dr. Richard O'Reilly of the Department of Pediatrics, Drs. Ronald Blasberg and Juri Tvujave of the Neuro-Oncology Laboratory, Dr. Michel Sadelain of the Department of Human Genetics, and Drs. Julius Balatoni and Ronald Finn of the Radiochemistry and Cyclotron Facility.)



Planar gamma camera image of [131I]-FIAU-labeled T cells 4 days post-injection in a SCID mouse, bearing a matched and an unmatched EBV lymphoma xenograft

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Tjuvajev JG, Avril N, Oku T, Sasajima T, Miyagawa T, Joshi R, Safer M, Beattie B, DiResta G, Daghighian F, Augensen F, Koutcher J, Zweit J, Humm J, Larson SM, Finn R, Blasberg R. Imaging herpes virus thymidine kinase gene transfer and expression by positron emission tomography. Cancer Res. 1998;58:4333-4341.

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