demonstrated significant accumulation of both antibodies in the tumors. Approximately 40% of the injected dose/g tissue accumulated in the tumors at 90–180 hours after injection, and tumor/blood ratios of 6 to 8 were seen with these antibodies. This accumulation was better than that seen with Prostascint ™ in the same model. Control antibodies did not accumulate in the LNCaP xenografts. Based on this specific accumulation of these antibodies and the selective expression of RG-1 protein, we suggest that antibodies 19G9 and 34E1 may be suitable for in vivo diagnosis and therapy of prostate cancer.

**294** POSTER

**1D09C3, a human, HLA-DR-specific monoclonal antibody efficiently induces programmed cell death in lymphoid tumors**

J.-B. Holz[1], Z. Nagy[1], B. Rattel[1], K. Lobenwein[1], S. Leyer[1], A. Krenn[1], S. Messemer[2], F. Schwaiger[2]. [1]*GPC Biotech AG, Drug Development, Munich, Germany;* [2]*Aurigon GmbH, Tutzing, Germany*

**Background:** Major histocompatibility complex class **II** molecules (MHC-**II**) are transmemebrane glycoproteins and are only expressed on the surface of immune system cells: B cells, macrophages and mature dendritic cells. In addition to their role of presenting antigen to T-lymphocytes they can serve as receptors triggering programmed cell death. It has been demonstrated, that MHC-**II** induced apoptosis affects activated/tumor transformed cells selectively and proceeds without the involvement of caspases. 1D09C3 is an IgG4 antibody derived from a human antibody phage display library, binding to human leukocyte antigen-DR (HLA-DR) with a sub-nM affinity. The selection of 1D09C3 from a panel of mAbs was based on its ability to kill a selected panel of human HLA-DR$^+$ lymphoma/leukemia cells in vitro while normal, resting HLA-DR$^+$ cells were not affected, thus resulting in a selectivity for the apoptotic effect.
**Material and Methods:** The in vivo activity of 1D09C3 has been investigated in xenotransplant models of Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell leukemia, and multiple myeloma. 1D09C3 was given at different doses ranging from 1mg/day to 0.04 μg/day in divided doses (iv) in a series of experiments. The dosing was carried out on days 5,7, and 9. To eliminate NK cells the SCID mice were pretreated with anti-asialo GM1 for three days, starting one day prior to the intravenous tumor cell inoculation. In the late stage disease experiments, 1D09C3 was administered for 4 or 5 days at 1 mg/day (iv) once visible symptoms of disseminated lymphoma were present. Rituximab was administered concurrently with 1D09C3 (iv) in a combination study to explore potentially synergistic effects in a non-Hodgkin's lymphoma model. The disease endpoint was paraplegia or death.
**Results:** The antibody showed very consistent activity across all four tumor models: within a dose range of 2,5 μg to 1 mg/day/mouse, the time to disease progression was delayed in all treated animals, compared to vehicle treated controls. High dose (1 mg/day × 4) treatment at late stages of disseminated lymphoma (~7 days before moribund) could still rescue 3/9 treated animals. The effect of 1D09C3 was compared to that of rituximab in a model of CD20$^+$HLA-DR$^+$ non-Hodgkin's lymphoma. The single agent efficacy of 1D09C3 was comparable to rituximab, however, when administered concurrently, the efficacy of the combination regimen exceeded the efficacy of either drug alone. In addition to malignant lymphoid cells, 1D09C3 has shown to induce death of HLA-DR$^+$ melanoma cells, in vivo studies are underway.
**Conclusion:** 1D09C3 has consistently demonstrated efficacy in various lymphoid tumors as well as in HLA-DR$^+$ melanoma cell lines. In a terminal-stage disseminated lymphoma model, high-dose treatment with 1D09C3 slowed down disease progression and resulted in 3 long term survivors (2 disease free and one with a single localized tumor) out of 9 treated animals. The combination of 1D09C3 with rituximab showed greater efficacy than either antibody alone in a non-Hodgkin's lymphoma model. The most likely basis for the observed increased efficacy is that the antibodies recognize different target receptors and may have different effector mechanisms.

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**Enhancing radioimmunotherapy with the PDGFr-beta inhibitor: imaging and tumor response studies**

J. Baranowska-Kortylewicz[1], M. Abe[1], T. Kurizaki[2], K. Pietras[3], Z.P. Kortylewicz[1], J. Nearman[1], R.L. Mosley[4], C.A. Enke[1], A. Östman[5]. [1]*University of Nebraska Medical Center, Radiation Oncology, Omaha, USA;* [2]*National Hospital Organization, Kumamoto Medical Center, Kumamoto City, Japan;* [3]*University of California, Diabetes Center, San Francisco, USA;* [4]*University of Nebraska Medical Center, Pathology and Microbiology, Omaha, USA;* [5]*Karolinska Institute, Pathology-Oncology, Stockholm, Sweden*

**Background:** The success of radioimmunotherapy (RIT) depends on the tumor-specific delivery of radioisotopes in quantities sufficient to deposit therapeutic radiation doses. In radiosensitive tumors such as lymphoma, this aim is accomplished with the total administered doses that spare normal tissues. Solid tumors are less sensitive to radiation than lymphomas, and as a result they are not responsive to RIT at tolerable doses. Recent studies indicate that the inhibition of PDGFr-β in the tumor stroma with STI571 attenuates tumor hypertension ($P_{IF}$) and improves influx of chemotherapy to tumors (1, 2). We proposed that a combination regimen of STI571 + RIT may well allow accumulation of therapeutically sufficient radiation doses in solid tumors.
**Materials and Methods:** All studies were conducted in a mouse model of the human colorectal adenocarcinoma LS 174T grown as subcutaneous (SQ) tumors in athymic mice. Radioimmunotherapy and radioimmunodiagnosis studies were conducted using a monoclonal antibody B72.3 that recognizes TAG-72 antigen common to nearly 90% of human adenocarcinomas (3,4). Imaging studies were done using the LumaGEM™ scintillation camera.
**Results:** STI571-induced attenuation of $P_{IF}$ had a positive effect on the total uptake as well as the homogeneity of $^{125}$I-B72.3 distribution within the tumor. This effect was dose-dependent and under optimized dosing conditions allowed for a 160% enhancement in the absolute tumor uptake of radiolabeled B72.3 as measured in the biodistribution studies. SPECT imaging studies substantiated these results and indicated that the homogeneity of radioisotope distribution was also significantly improved when compared with the control tumors. The increased uptake of RIT into the tumor resulted in >400% increase in the tumor absorbed radiation doses in STI571+RIT-treated mice compared to PBS-treated mice. Two additional causes related to the STI571-induced attenuation of $P_{IF}$, were identified: improved homogeneity of MAb distribution in tumor; and increased tumor radiosensitivity in response to improved tumor oxygenation.
**Conclusions:** The attenuation of tumor $P_{IF}$ was identified as the primary reason for the enhanced radioimmunoconjugate uptake and improved RIT of the STI571-treated tumors.

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**296** POSTER

**Trastuzumab monoclonal antibody labeled with alpha-particle emitter astatine: targeted radiotherapeutic experiments on a HER2-positive breast carcinomatous meningitis animal model after intrathecal administration**

A. Boskovitz[1], H. Ochiai[2], T. Okamura[1], X.-G. Zhao[3], D. Bigner[1], M. Zalutsky[3]. [1]*Duke University Medical Center, Dept. of Pathology – Neuro-Oncology Program, Durham, NC, USA;* [2]*Duke University Medical Center, Dept. of Surgery – Neuro-Oncology Program, Durham, NC, USA;* [3]*Duke University Medical Center, Dept. of Radiology – Neuro-Oncology Program, Durham, NC, USA*

Carcinomatous meningitis (CM) is a devastating disease that results from the dissemination of tumor cells into the subarachnoid space along the brain and spine. Breast carcinoma is one of the two most frequent non-CNS origin of CM. Systemic treatment with the monoclonal antibody (mAB) trastuzumab (Herceptin®) is efficient against HER2-positive breast carcinoma and systemic metastasis but does not affect the course of the leptomeningeal disease as the CSF concentration remains 300-fold lower than the systemic one. Intrathecal administration of radiolabeled trastuzumab could result in the delivery of a high radiation dose specifically to the disseminated tumor foci, while reducing systemic exposure. Astatine $^{211}$At emits α-particles with a high linear energy transfer (97 keV/μm), a