

APPLICATION OF PIMONIDAZOLE – MALIGNANT TISSUE

2. Tumors – Experimental

Brain

1. Bernsen HJ, Rijken PF, Peters JP, et al. Suramin treatment of human glioma xenografts; effects on tumor vasculature and oxygenation status. *J Neurooncol* 1999; 44: 129-36.
2. Bernsen HJ, Rijken PF, Peters H, et al. Hypoxia in a human intracerebral glioma model. *J Neurosurg* 2000; 93: 449-54.
3. Olive PL, Durand RE, Raleigh JA, Luo C, Aquino-Parsons C. Comparison between the comet assay and pimonidazole binding for measuring tumour hypoxia. *Br J Cancer* 2000; 83: 1525-31.
4. Rijken PF, Bernsen HJ, Peters JP, Hodgkiss RJ, Raleigh JA, van der Kogel AJ. Spatial relationship between hypoxia and the (perfused) vascular network in a human glioma xenograft: a quantitative multi-parameter analysis. *Int J Radiat Oncol Biol Phys* 2000; 48: 571-82.
5. Eikesdal HP, Bjerkvig R, Raleigh JA, Mella O, Dahl O. Tumor vasculature is targeted by the combination of combretastatin A-4 and hyperthermia. *Radiother Oncol* 2001; 61: 313-20.
6. Rijken PF, Peters JP, Van der Kogel AJ. Quantitative analysis of varying profiles of hypoxia in relation to functional vessels in different human glioma xenograft lines. *Radiat Res* 2002; 157: 626-32.
7. Sminia P, Acker H, Eikesdal HP, et al. Oxygenation and response to irradiation of organotypic multicellular spheroids of human glioma. *Anticancer Res* 2003; 23: 1461-6.
8. Zoula S, Rijken PF, Peters JP, et al. Pimonidazole binding in C6 rat brain glioma: relation with lipid droplet detection. *Br J Cancer* 2003; 88: 1439-44.
9. Cardenas-Navia LI, Yu D, Braun RD, Brizel DM, Secomb TW, Dewhirst MW. Tumor-dependent kinetics of partial pressure of oxygen fluctuations during air and oxygen breathing. *Cancer Res* 2004; 64: 6010-7.
10. Kostourou V, Troy H, Murray JF, et al. Overexpression of dimethylarginine dimethylaminohydrolase enhances tumor hypoxia: an insight into the relationship of hypoxia and angiogenesis in vivo. *Neoplasia* 2004; 6: 401-11.
11. Post DE, Devi NS, Li Z, et al. Cancer therapy with a replicating oncolytic adenovirus targeting the hypoxic microenvironment of tumors. *Clin Cancer Res* 2004; 10: 8603-12.

12. Prabhakaran K, Sampson DA, Hoehner JC. Neuroblastoma survival and death: an in vitro model of hypoxia and metabolic stress. *J Surg Res* 2004; 116: 288-96.
13. Greco O, Joiner MC, Doleh A, Powell AD, Hillman GG, Scott SD. Hypoxia- and radiation-activated Cre/loxP 'molecular switch' vectors for gene therapy of cancer. *Gene Ther* 2006; 13: 206-15.
14. Jensen RL. Hypoxia in the tumorigenesis of gliomas and as a potential target for therapeutic measures. *Neurosurg Focus* 2006; 20: E24.
15. Kang SH, Cho HT, Devi S, et al. Antitumor effect of 2-methoxyestradiol in a rat orthotopic brain tumor model. *Cancer Res* 2006; 66: 11991-7.
16. Yuan H, Schroeder T, Bowsher JE, Hedlund LW, Wong T, Dewhirst MW. Intertumoral differences in hypoxia selectivity of the PET imaging agent ⁶⁴Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone). *J Nucl Med* 2006; 47: 989-98.
17. Kumar S, Brown SL, Kolozsvary A, Freytag SO, Kim JH. Efficacy of suicide gene therapy in hypoxic rat 9L glioma cells. *J Neurooncol* 2008.
18. Scigliano S, Pinel S, Poussier S, et al. Measurement of hypoxia using invasive oxygen-sensitive electrode, pimonidazole binding and ¹⁸F-FDG uptake in anaemic or erythropoietin-treated mice bearing human glioma xenografts. *Int J Oncol* 2008; 32: 69-77.
19. Yeom CJ, Chung JK, Kang JH, et al. Visualization of Hypoxia-Inducible Factor-1 Transcriptional Activation in C6 Glioma Using Luciferase and Sodium Iodide Symporter Genes. *J Nucl Med* 2008.
20. Zhao D, Najbauer J, Garcia E, et al. Neural stem cell tropism to glioma: critical role of tumor hypoxia. *Mol Cancer Res* 2008; 6: 1819-29.

21. Zaghoul N, Hernandez SL, Bae JO, et al. Vascular endothelial growth factor blockade rapidly elicits alternative proangiogenic pathways in neuroblastoma. *Int J Oncol* 2009; 34: 401-7.
22. McGee MC, Hamner JB, Williams RF, et al. Improved intratumoral oxygenation through vascular normalization increases glioma sensitivity to ionizing radiation. *Int J Radiat Oncol Biol Phys* 2010; 76: 1537-45.
23. Foti R, Zucchelli S, Biagioli M, et al. Parkinson disease-associated DJ-1 is required for the expression of the glial cell line-derived neurotrophic factor receptor RET in human neuroblastoma cells. *J Biol Chem* 2010; 285: 18565-74.
24. Boulton JK, Walker-Samuel S, Jamin Y, Leiper JM, Whitley GS, Robinson SP. Active site mutant dimethylarginine dimethylaminohydrolase 1 expression confers an intermediate tumour phenotype in C6 gliomas. *J Pathol* 2011.
25. Burrell JS, Walker-Samuel S, Baker LC, et al. Evaluation of novel combined carbogen USPIO (CUSPIO) imaging biomarkers in assessing the antiangiogenic effects of cediranib (AZD2171) in rat C6 gliomas. *Int J Cancer* 2012; 131: 1854-62.

26. Lemasson B, Christen T, Serduc R, et al. Evaluation of the Relationship between MR Estimates of Blood Oxygen Saturation and Hypoxia: Effect of an Antiangiogenic Treatment on a Gliosarcoma Model. *Radiology* 2012.

Breast

1. Samoszuk M, Corwin MA. Mast cell inhibitor cromolyn increases blood clotting and hypoxia in murine breast cancer. *Int J Cancer* 2003; 107: 159-63.
2. Franco M, Man S, Chen L, et al. Targeted anti-vascular endothelial growth factor receptor-2 therapy leads to short-term and long-term impairment of vascular function and increase in tumor hypoxia. *Cancer Res* 2006; 66: 3639-48.
3. Greco O, Joiner MC, Doleh A, Powell AD, Hillman GG, Scott SD. Hypoxia- and radiation-activated Cre/loxP 'molecular switch' vectors for gene therapy of cancer. *Gene Ther* 2006; 13: 206-15.
4. Kirkpatrick JP, Hardee ME, Snyder SA, et al. The effect of darbepoetin alfa on growth, oxygenation and radioresponsiveness of a breast adenocarcinoma. *Radiat Res* 2006; 165: 192-201.
5. Lipnik K, Greco O, Scott S, et al. Hypoxia- and radiation-inducible, breast cell-specific targeting of retroviral vectors. *Virology* 2006; 349: 121-33.
6. Fang Y, Sullivan R, Graham CH. Confluence-dependent resistance to doxorubicin in human MDA-MB-231 breast carcinoma cells requires hypoxia-inducible factor-1 activity. *Exp Cell Res* 2007; 313: 867-77.
7. Karantza-Wadsworth V, Patel S, Kravchuk O, et al. Autophagy mitigates metabolic stress and genome damage in mammary tumorigenesis. *Genes Dev* 2007; 21: 1621-35.
8. Zhao D, Chang CH, Kim JG, Liu H, Mason RP. In vivo near-infrared spectroscopy and magnetic resonance imaging monitoring of tumor response to combretastatin A-4-phosphate correlated with therapeutic outcome. *Int J Radiat Oncol Biol Phys* 2011; 80: 574-81.
9. Przybyla BD, Shafirstein G, Koonce NA, Webber JS, Griffin RJ. Conductive thermal ablation of 4T1 murine breast carcinoma reduces severe hypoxia in surviving tumour. *Int J Hyperthermia* 2012; 28: 156-62.
10. Conley SJ, Gheordunescu E, Kakarala P, et al. Antiangiogenic agents increase breast cancer stem cells via the generation of tumor hypoxia. *Proc Natl Acad Sci U S A* 2012; 109: 2784-9.

Colorectal

1. Pedley RB, El-Emir Eb, Flynn AA, et al. Synergy between vascular targeting agents and antibody-directed therapy. *Int J Radiat Oncol Biol Phys* 2002; 54: 1524-31.

2. Huxham LA, Kyle AH, Baker JH, Nykilchuk LK, Minchinton AI. Microregional effects of gemcitabine in HCT-116 xenografts. *Cancer Res* 2004; 64: 6537-41.
3. Nelson DW, Cao H, Zhu Y, et al. A noninvasive approach for assessing tumor hypoxia in xenografts: developing a urinary marker for hypoxia. *Cancer Res* 2005; 65: 6151-8.
4. Ceelen W, Smeets P, Backes W, et al. Noninvasive monitoring of radiotherapy-induced microvascular changes using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) in a colorectal tumor model. *Int J Radiat Oncol Biol Phys* 2006; 64: 1188-96.
5. Li XF, Carlin S, Urano M, Russell J, Ling CC, O'Donoghue JA. Visualization of hypoxia in microscopic tumors by immunofluorescent microscopy. *Cancer Res* 2007; 67: 7646-53.
6. Shahrzad S, Bertrand K, Minhas K, Coomber BL. Induction of DNA hypomethylation by tumor hypoxia. *Epigenetics* 2007; 2: 119-25.
7. Shin KH, Diaz-Gonzalez JA, Russell J, et al. Detecting changes in tumor hypoxia with carbonic anhydrase IX and pimonidazole. *Cancer Biol Ther* 2007; 6: 70-5.
8. van der Bilt JD, Soeters ME, Duyverman AM, et al. Perinecrotic hypoxia contributes to ischemia/reperfusion-accelerated outgrowth of colorectal micrometastases. *Am J Pathol* 2007; 170: 1379-88.
9. He F, Deng X, Wen B, et al. Noninvasive molecular imaging of hypoxia in human xenografts: comparing hypoxia-induced gene expression with endogenous and exogenous hypoxia markers. *Cancer Res* 2008; 68: 8597-606.
10. Kalber TL, Waterton JC, Griffiths JR, Ryan AJ, Robinson SP. Longitudinal in vivo susceptibility contrast MRI measurements of LS174T colorectal liver metastasis in nude mice. *J Magn Reson Imaging* 2008; 28: 1451-8.
11. Selvakumaran M, Yao KS, Feldman MD, O'Dwyer PJ. Antitumor effect of the angiogenesis inhibitor bevacizumab is dependent on susceptibility of tumors to hypoxia-induced apoptosis. *Biochem Pharmacol* 2008; 75: 627-38.
12. Ahlskog JK, Schliemann C, Marlind J, et al. Human monoclonal antibodies targeting carbonic anhydrase IX for the molecular imaging of hypoxic regions in solid tumours. *Br J Cancer* 2009; 101: 645-57.
13. Russell J, Carlin S, Burke SA, Wen B, Yang KM, Ling CC. Immunohistochemical detection of changes in tumor hypoxia. *Int J Radiat Oncol Biol Phys* 2009; 73: 1177-86.
14. Li XF, Sun X, Ma Y, et al. Detection of hypoxia in microscopic tumors using ¹³¹I-labeled iodo-azomycin galactopyranoside (¹³¹I-IAZGP) digital autoradiography. *Eur J Nucl Med Mol Imaging* 2010; 37: 339-48.
15. Oehler C, O'Donoghue JA, Russell J, et al. ¹⁸F-fluoromisonidazole PET imaging as a biomarker for the response to 5,6-dimethylxanthenone-4-acetic acid in colorectal xenograft tumors. *J Nucl Med* 2011; 52: 437-44.
16. Vangestel C, Van de Wiele C, Van Damme N, et al. (99mTc-(CO)(3)His-annexin A5 micro-SPECT demonstrates increased cell death by

irinotecan during the vascular normalization window caused by bevacizumab. *J Nucl Med* 2011; 52: 1786-94.

Gastric

1. Takahashi M, Yasui H, Ogura A, et al. X Irradiation Combined with TNF alpha-related Apoptosis-inducing Ligand (TRAIL) Reduces Hypoxic Regions of Human Gastric Adenocarcinoma Xenografts in SCID Mice. *J Radiat Res (Tokyo)* 2008; 49: 153-61.

Lung

1. Kim MS, Kwon HJ, Lee YM, et al. Histone deacetylases induce angiogenesis by negative regulation of tumor suppressor genes. *Nat Med* 2001; 7: 437-43.

2. Huang G, Chen L. Discrepancies between antiangiogenic and antitumor effects of recombinant human endostatin. *Cancer Biother Radiopharm* 2009; 24: 589-96.

3. Oh M, Tanaka T, Kobayashi M, et al. Radio-copper-labeled Cu-ATSM: an indicator of quiescent but clonogenic cells under mild hypoxia in a Lewis lung carcinoma model. *Nucl Med Biol* 2009; 36: 419-26.

4. Graves EE, Vilalta M, Cecic IK, et al. Hypoxia in models of lung cancer: implications for targeted therapeutics. *Clin Cancer Res* 2010; 16: 4843-52.

5. Lee JC, Kinniry PA, Arguiri E, et al. Dietary curcumin increases antioxidant defenses in lung, ameliorates radiation-induced pulmonary fibrosis, and improves survival in mice. *Radiat Res* 2010; 173: 590-601.

Melanoma

1. Lyng H, Sundfor K, Rofstad EK. Oxygen tension in human tumours measured with polarographic needle electrodes and its relationship to vascular density, necrosis and hypoxia. *Radiother Oncol* 1997; 44: 163-9.

2. Rofstad EK, Maseide K. Radiobiological and immunohistochemical assessment of hypoxia in human melanoma xenografts: acute and chronic hypoxia in individual tumours. *Int J Radiat Biol* 1999; 75: 1377-93.

3. Danielsen T, Rofstad EK. The constitutive level of vascular endothelial growth factor (VEGF) is more important than hypoxia-induced VEGF up-regulation in the angiogenesis of human melanoma xenografts. *Br J Cancer* 2000; 82: 1528-34.

4. Rofstad EK, Halsor EF. Hypoxia-associated spontaneous pulmonary metastasis in human melanoma xenografts: involvement of microvascular hot spots induced in hypoxic foci by interleukin 8. *Br J Cancer* 2002; 86: 301-8.

5. Rofstad EK, Rasmussen H, Galappathi K, Mathiesen B, Nilsen K, Graff BA. Hypoxia promotes lymph node metastasis in human melanoma xenografts by up-regulating the urokinase-type plasminogen activator receptor. *Cancer Res* 2002; 62: 1847-53.
6. Rofstad EK, Tunheim SH, Mathiesen B, et al. Pulmonary and lymph node metastasis is associated with primary tumor interstitial fluid pressure in human melanoma xenografts. *Cancer Res* 2002; 62: 661-4.
7. Rofstad EK, Mathiesen B, Galappathi K. Increased metastatic dissemination in human melanoma xenografts after subcurative radiation treatment: radiation-induced increase in fraction of hypoxic cells and hypoxia-induced up-regulation of urokinase-type plasminogen activator receptor. *Cancer Res* 2004; 64: 13-8.
8. Liu J, Qu R, Ogura M, Shibata T, Harada H, Hiraoka M. Real-time Imaging of Hypoxia-inducible Factor-1 Activity in Tumor Xenografts. *J Radiat Res (Tokyo)* 2005; 46: 93-102.
9. Rofstad EK, Mathiesen B, Henriksen K, Kindem K, Galappathi K. The Tumor Bed Effect: increased metastatic dissemination from hypoxia-Induced up-regulation of metastasis-promoting gene products. *Cancer Res* 2005; 65: 2387-96.
10. Stockwin LH, Blonder J, Bumke MA, et al. Proteomic analysis of plasma membrane from hypoxia-adapted malignant melanoma. *J Proteome Res* 2006; 5: 2996-3007.
11. Rofstad EK, Galappathi K, Mathiesen B, Ruud EB. Fluctuating and diffusion-limited hypoxia in hypoxia-induced metastasis. *Clin Cancer Res* 2007; 13: 1971-8.
12. Shahrzad S, Bertrand K, Minhas K, Coomber BL. Induction of DNA hypomethylation by tumor hypoxia. *Epigenetics* 2007; 2: 119-25.
13. Gulliksrud K, Vestvik IK, Galappathi K, Mathiesen B, Rofstad EK. Detection of different hypoxic cell subpopulations in human melanoma xenografts by pimonidazole immunohistochemistry. *Radiat Res* 2008; 170: 638-50.
14. Gulliksrud K, Mathiesen B, Galappathi K, Rofstad EK. Quantitative assessment of hypoxia in melanoma xenografts by dynamic contrast-enhanced magnetic resonance imaging: intradermal versus intramuscular tumors. *Radiother Oncol* 2010; 97: 233-8.
15. Rofstad EK, Mathiesen B. Metastasis in melanoma xenografts is associated with tumor microvascular density rather than extent of hypoxia. *Neoplasia* 2010; 12: 889-98.
16. Simonsen TG, Gaustad JV, Rofstad EK. Development of hypoxia in a preclinical model of tumor micrometastases. *Int J Radiat Oncol Biol Phys* 2010; 76: 879-88.
17. Egeland TA, Gulliksrud K, Gaustad JV, Mathiesen B, Rofstad EK. Dynamic contrast-enhanced-MRI of tumor hypoxia. *Magn Reson Med* 2011.
18. Gulliksrud K, Ovrebo KM, Mathiesen B, Rofstad EK. Differentiation between hypoxic and non-hypoxic experimental tumors by dynamic

contrast-enhanced magnetic resonance imaging. *Radiother Oncol* 2011; 98: 360-4.

19. Egeland TA, Gulliksrud K, Gaustad JV, Mathiesen B, Rofstad EK. Dynamic contrast-enhanced-MRI of tumor hypoxia. *Magn Reson Med* 2012; 67: 519-30.

20. Ellingsen C, Ovrebo KM, Galappathi K, Mathiesen B, Rofstad EK. pO₂ fluctuation pattern and cycling hypoxia in human cervical carcinoma and melanoma xenografts. *Int J Radiat Oncol Biol Phys* 2012; 83: 1317-23.

21. Gaustad JV, Simonsen TG, Leinaas MN, Rofstad EK. Sunitinib treatment does not improve blood supply but induces hypoxia in human melanoma xenografts. *BMC Cancer* 2012; 12: 388.

22. Ovrebo KM, Ellingsen C, Galappathi K, Rofstad EK. Dynamic contrast-enhanced magnetic resonance imaging of the metastatic potential of melanoma xenografts. *Int J Radiat Oncol Biol Phys* 2012; 83: e121-7.

Multiple Myeloma

1. Asosingh K, De Raeve H, de Ridder M, et al. Role of the hypoxic bone marrow microenvironment in 5T2MM murine myeloma tumor progression. *Haematologica* 2005; 90: 810-7.

2. Hu J, Handisides DR, Van Valckenborgh E, et al. Targeting the multiple myeloma hypoxic niche with TH-302, a hypoxia-activated prodrug. *Blood* 2010; 116: 1524-7.

Non-small Cell Lung Carcinoma

1. McClelland MR, Carskadon SL, Zhao L, et al. Diversity of the angiogenic phenotype in non-small cell lung cancer. *Am J Respir Cell Mol Biol* 2007; 36: 343-50.

2. Graves EE, Vilalta M, Cecic IK, et al. Hypoxia in models of lung cancer: implications for targeted therapeutics. *Clin Cancer Res* 2010; 16: 4843-52.

3. Huang T, Civelek AC, Li J, et al. Tumor microenvironment-dependent 18F-FDG, 18F-fluorothymidine, and 18F-misonidazole uptake: a pilot study in mouse models of human non-small cell lung cancer. *J Nucl Med* 2012; 53: 1262-8.

Pancreatic Cancer

2. Okuda K, Okabe Y, Kadonosono T, et al. 2-Nitroimidazole-Tricarbocyanine Conjugate as a Near-Infrared Fluorescent Probe for in Vivo Imaging of Tumor Hypoxia. *Bioconjugate Chem* 2012; 23: 324-9.

Prostatic Cancer

1. Pollard M, Suckow MA. Hormone-refractory prostate cancer in the Lobund-Wistar rat. *Exp Biol Med (Maywood)* 2005; 230: 520-6.

2. Hammarsten P, Halin S, Wikstom P, Henriksson R, Rudolfsson SH, Bergh A. Inhibitory effects of castration in an orthotopic model of androgen-independent prostate cancer can be mimicked and enhanced by angiogenesis inhibition. *Clin Cancer Res* 2006; 12: 7431-6.
3. Carlin S, Pugachev A, Sun X, et al. In vivo characterization of a reporter gene system for imaging hypoxia-induced gene expression. *Nucl Med Biol* 2009; 36: 821-31.
4. Ma J, Waxman DJ. Dominant effect of antiangiogenesis in combination therapy involving cyclophosphamide and axitinib. *Clin Cancer Res* 2009; 15: 578-88.
5. Kimura M, Rabbani Z, Mouraviev V, et al. Role of vitamin D(3) as a sensitizer to cryoablation in a murine prostate cancer model: preliminary in vivo study. *Urology* 2010; 76: 764 e14-20.
6. Kimura M, Rabbani Z, Mouraviev V, et al. Morphology of hypoxia following cryoablation in a prostate cancer murine model: its relationship to necrosis, apoptosis and, microvessel density. *Cryobiology* 2010; 61: 148-54.
7. Hagtvet E, Roe K, Olsen DR. Liposomal doxorubicin improves radiotherapy response in hypoxic prostate cancer xenografts. *Radiat Oncol* 2011; 6: 135.
8. Baker LC, Boulton JK, Walker-Samuel S, et al. The HIF-pathway inhibitor NSC-134754 induces metabolic changes and anti-tumour activity while maintaining vascular function. *Br J Cancer* 2012; 106: 1638-47.
9. Roe K, Mikalsen LT, van der Kogel AJ, et al. Vascular responses to radiotherapy and androgen-deprivation therapy in experimental prostate cancer. *Radiat Oncol* 2012; 7: 75.

Renal Cell Carcinoma

1. van Wijngaarden J, de Rooij K, van Beek E, et al. Identification of differentially expressed genes in a renal cell carcinoma tumor model after endostatin-treatment. *Lab Invest* 2004; 84: 1472-83.
2. Murakami M, Zhao S, Zhao Y, et al. Evaluation of changes in the tumor microenvironment after sorafenib therapy by sequential histology and 18F-fluoromisonidazole hypoxia imaging in renal cell carcinoma. *Int J Oncol* 2012; 41: 1593-600.

Retinoblastoma

1. Boutrid H, Jockovich ME, Murray TG, et al. Targeting hypoxia, a novel treatment for advanced retinoblastoma. *Invest Ophthalmol Vis Sci* 2008; 49: 2799-805.
2. Boutrid H, Pina Y, Cebulla CM, et al. Increased hypoxia following vessel targeting in a murine model of retinoblastoma. *Invest Ophthalmol Vis Sci* 2009; 50: 5537-43.

3. Pina Y, Houston SK, Murray TG, et al. Focal, periocular delivery of 2-deoxy-D-glucose as adjuvant to chemotherapy for treatment of advanced retinoblastoma. *Invest Ophthalmol Vis Sci* 2010; 51: 6149-56.

Sarcoma

1. Laurent F, Benard P, Canal P, Soula G. Autoradiographic distribution of [14C]-labelled pimonidazole in rhabdomyosarcoma-bearing rats and pigmented mice. *Cancer Chemother Pharmacol* 1988; 22: 308-15.
2. Cobb LM, Nolan J, Butler SA. Distribution of pimonidazole and RSU 1069 in tumour and normal tissues. *Br J Cancer* 1990; 62: 915-8.
3. Pogue BW, Paulsen KD, O'Hara JA, Wilmot CM, Swartz HM. Estimation of oxygen distribution in RIF-1 tumors by diffusion model-based interpretation of pimonidazole hypoxia and eppendorf measurements. *Radiat Res* 2001; 155: 15-25.
4. Cardenas-Navia LI, Yu D, Braun RD, Brizel DM, Secomb TW, Dewhirst MW. Tumor-dependent kinetics of partial pressure of oxygen fluctuations during air and oxygen breathing. *Cancer Res* 2004; 64: 6010-7.
5. Davies Cd, Lundstrom LM, Frengen J, et al. Radiation improves the distribution and uptake of liposomal doxorubicin (caelyx) in human osteosarcoma xenografts. *Cancer Res* 2004; 64: 547-53.
6. Dubois L, Landuyt W, Haustermans K, et al. Evaluation of hypoxia in an experimental rat tumour model by [(18)F]fluoromisonidazole PET and immunohistochemistry. *Br J Cancer* 2004; 91: 1947-54.
7. Doege K, Heine S, Jensen I, Jelkmann W, Metzen E. Inhibition of mitochondrial respiration elevates oxygen concentration but leaves regulation of hypoxia-inducible factor (HIF) intact. *Blood* 2005; 106: 2311-7.
8. van der Schaft DWJ, Hillen F, Pauwels P, et al. Tumor Cell Plasticity in Ewing Sarcoma, an Alternative Circulatory System Stimulated by Hypoxia. *Cancer Res* 2005; 65: 11520-8.
9. Kleiter MM, Thrall DE, Malarkey DE, et al. A comparison of oral and intravenous pimonidazole in canine tumors using intravenous CCI-103F as a control hypoxia marker. *Int J Radiat Oncol Biol Phys* 2006; 64: 592-602.
10. Yuan H, Schroeder T, Bowsher JE, Hedlund LW, Wong T, Dewhirst MW. Intertumoral differences in hypoxia selectivity of the PET imaging agent 64Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone). *J Nucl Med* 2006; 47: 989-98.
11. Busk M, Horsman MR, Jakobsen S, et al. Imaging Hypoxia in Xenografted and Murine Tumors With (18)F-Fluoroazomycin Arabinoside: A Comparative Study Involving microPET, Autoradiography, Po(2)-Polarography, and Fluorescence Microscopy. *Int J Radiat Oncol Biol Phys* 2008; 70: 1202-12.
12. Sersa G, Jarm T, Kotnik T, et al. Vascular disrupting action of electroporation and electrochemotherapy with bleomycin in murine sarcoma. *Br J Cancer* 2008; 98: 388-98.

13. Laifenfeld D, Gilchrist A, Drubin D, et al. The role of hypoxia in 2-butoxyethanol-induced hemangiosarcoma. *Toxicol Sci* 2010; 113: 254-66.
14. Dubois LJ, Lieuwes NG, Janssen MH, et al. Preclinical evaluation and validation of [18F]HX4, a promising hypoxia marker for PET imaging. *Proc Natl Acad Sci U S A* 2011; 108: 14620-5.
15. Criswell KA, Cook JC, Morse D, et al. Pregabalin induces hepatic hypoxia and increases endothelial cell proliferation in mice, a process inhibited by dietary vitamin E supplementation. *Toxicol Sci* 2012; 128: 42-56.
16. D'Andrea FP, Safwat A, Burns JS, Kassem M, Horsman MR, Overgaard J. Tumour microenvironment and radiation response in sarcomas originating from tumourigenic human mesenchymal stem cells. *Int J Radiat Biol* 2012; 88: 457-65.
17. Hansen AE, Kristensen AT, Jorgensen JT, et al. (64)Cu-ATSM and (18)FDG PET uptake and (64)Cu-ATSM autoradiography in spontaneous canine tumors: comparison with pimonidazole hypoxia immunohistochemistry. *Radiat Oncol* 2012; 7: 89.
18. Lemasson B, Christen T, Serduc R, et al. Evaluation of the Relationship between MR Estimates of Blood Oxygen Saturation and Hypoxia: Effect of an Antiangiogenic Treatment on a Gliosarcoma Model. *Radiology* 2012.

Squamous Cell Carcinoma

1. Bussink J, Kaanders JH, Rijken PF, Raleigh JA, Van der Kogel AJ. Changes in blood perfusion and hypoxia after irradiation of a human squamous cell carcinoma xenograft tumor line. *Radiat Res* 2000; 153: 398-404.
2. Ljungkvist AS, Bussink J, Rijken PF, Raleigh JA, Denekamp J, Van Der Kogel AJ. Changes in tumor hypoxia measured with a double hypoxic marker technique. *Int J Radiat Oncol Biol Phys* 2000; 48: 1529-38.
3. Petersen C, Eicheler W, Frommel A, et al. Proliferation and micromilieu during fractionated irradiation of human FaDu squamous cell carcinoma in nude mice. *Int J Radiat Biol* 2003; 79: 469-77.
4. Bennewith KL, Durand RE. Quantifying transient hypoxia in human tumor xenografts by flow cytometry. *Cancer Res* 2004; 64: 6183-9.
5. Bhattacharya A, Toth K, Mazurchuk R, et al. Lack of microvessels in well-differentiated regions of human head and neck squamous cell carcinoma A253 associated with functional magnetic resonance imaging detectable hypoxia, limited drug delivery, and resistance to irinotecan therapy. *Clin Cancer Res* 2004; 10: 8005-17.
6. Nelson DW, Cao H, Zhu Y, et al. A noninvasive approach for assessing tumor hypoxia in xenografts: developing a urinary marker for hypoxia. *Cancer Res* 2005; 65: 6151-8.
7. O'Donoghue J A, Zanzonico P, Pugachev A, et al. Assessment of regional tumor hypoxia using (18)F-fluoromisonidazole and (64)Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone) positron emission tomography:

Comparative study featuring microPET imaging, Po(2) probe measurement, autoradiography, and fluorescent microscopy in the R3327-AT and FaDu rat tumor models. *Int J Radiat Oncol Biol Phys* 2005; 61: 1493-502.

8. Solomon B, Binns D, Roselt P, et al. Modulation of intratumoral hypoxia by the epidermal growth factor receptor inhibitor gefitinib detected using small animal PET imaging. *Mol Cancer Ther* 2005; 4: 1417-22.

9. van Herpen CM, Bussink J, van der Kogel AJ, et al. Interleukin-12 has no effect on vascular density, perfusion, hypoxia and proliferation of an implanted human squamous cell carcinoma xenograft tumour despite up-regulation of ICAM-1. *Anticancer Res* 2005; 25: 1015-10121.

10. Yaromina A, Holscher T, Eichele W, et al. Does heterogeneity of pimonidazole labelling correspond to the heterogeneity of radiation-response of FaDu human squamous cell carcinoma? *Radiother Oncol* 2005; 76: 206-12.

11. Troost EG, Laverman P, Kaanders JH, et al. Imaging hypoxia after oxygenation-modification: Comparing [(18)F]FMISO autoradiography with pimonidazole immunohistochemistry in human xenograft tumors. *Radiother Oncol* 2006.

12. Yaromina A, Zips D, Thames HD, et al. Pimonidazole labelling and response to fractionated irradiation of five human squamous cell carcinoma (hSCC) lines in nude mice: The need for a multivariate approach in biomarker studies. *Radiother Oncol* 2006; 81: 122-9.

13. Matsumoto K, Szajek L, Krishna MC, et al. The influence of tumor oxygenation on hypoxia imaging in murine squamous cell carcinoma using [64Cu]Cu-ATSM or [18F]Fluoromisonidazole positron emission tomography. *Int J Oncol* 2007; 30: 873-81.

14. Bayer C, Schilling D, Hoetzel J, et al. PAI-1 levels predict response to fractionated irradiation in 10 human squamous cell carcinoma lines of the head and neck. *Radiother Oncol* 2008; 86: 361-8.

15. Busk M, Horsman MR, Jakobsen S, et al. Imaging Hypoxia in Xenografted and Murine Tumors With (18)F-Fluoroazomycin Arabinoside: A Comparative Study Involving microPET, Autoradiography, Po(2)-Polarography, and Fluorescence Microscopy. *Int J Radiat Oncol Biol Phys* 2008; 70: 1202-12.

16. Busk M, Horsman MR, Overgaard J. Resolution in PET hypoxia imaging: voxel size matters. *Acta Oncol* 2008; 47: 1201-10.

17. Miyazaki Y, Hara A, Kato K, et al. The effect of hypoxic microenvironment on matrix metalloproteinase expression in xenografts of human oral squamous cell carcinoma. *Int J Oncol* 2008; 32: 145-51.

18. Troost EG, Laverman P, Philippens ME, et al. Correlation of [18F]FMISO autoradiography and pimonidazole immunohistochemistry in human head and neck carcinoma xenografts. *Eur J Nucl Med Mol Imaging* 2008; 35: 1803-11.

19. Bruechner K, Bergmann R, Santiago A, et al. Comparison of [(18)F]FDG uptake and distribution with hypoxia and proliferation in FaDu

human squamous cell carcinoma (hSCC) xenografts after single dose irradiation. *Int J Radiat Biol* 2009; 1-9.

20. Ellingsen C, Natvig I, Gaustad JV, Gulliksrud K, Egeland TA, Rofstad EK. Human cervical carcinoma xenograft models for studies of the physiological microenvironment of tumors. *J Cancer Res Clin Oncol* 2009.

21. Yaromina A, Quennet V, Zips D, et al. Co-localisation of hypoxia and perfusion markers with parameters of glucose metabolism in human squamous cell carcinoma (hSCC) xenografts. *Int J Radiat Biol* 2009; 85: 972-80.

22. Busk M, Munk OL, Jakobsen S, et al. Assessing hypoxia in animal tumor models based on pharmacokinetic analysis of dynamic FAZA PET. *Acta Oncol* 2010; 49: 922-33.

23. Santiago A, Eicheler W, Bussink J, et al. Effect of cetuximab and fractionated irradiation on tumour micro-environment. *Radiother Oncol* 2010; 97: 322-9.

24. Yaromina A, Thames H, Zhou X, et al. Radiobiological hypoxia, histological parameters of tumour microenvironment and local tumour control after fractionated irradiation. *Radiother Oncol* 2010; 96: 116-22.

25. Maftai CA, Bayer C, Shi K, Astner ST, Vaupel P. Changes in the fraction of total hypoxia and hypoxia subtypes in human squamous cell carcinomas upon fractionated irradiation: Evaluation using pattern recognition in microcirculatory supply units. *Radiother Oncol* 2011.

26. Maftai CA, Shi K, Bayer C, Astner ST, Vaupel P. Comparison of (immuno-)fluorescence data with serial [(1)F]Fmiso PET/CT imaging for assessment of chronic and acute hypoxia in head and neck cancers. *Radiother Oncol* 2011; 99: 412-7.

27. Vigneswaran N, Wu J, Song A, Annapragada A, Zacharias W. Hypoxia-induced autophagic response is associated with aggressive phenotype and elevated incidence of metastasis in orthotopic immunocompetent murine models of head and neck squamous cell carcinomas (HNSCC). *Exp Mol Pathol* 2011; 90: 215-25.

28. Yaromina A, Kroeber T, Meinzer A, et al. Exploratory study of the prognostic value of microenvironmental parameters during fractionated irradiation in human squamous cell carcinoma xenografts. *Int J Radiat Oncol Biol Phys* 2011; 80: 1205-13.

29. Zaleska K, Bruechner K, Baumann M, Zips D, Yaromina A. Tumour-infiltrating CD11b+ myelomonocytes and response to fractionated irradiation of human squamous cell carcinoma (hSCC) xenografts. *Radiother Oncol* 2011.

30. Bayer C, Kielow A, Schilling D, et al. Monitoring PAI-1 and VEGF Levels in 6 Human Squamous Cell Carcinoma Xenografts During Fractionated Irradiation. *Int J Radiat Oncol Biol Phys* 2012; 84: e409-17.

31. Maftai CA, Bayer C, Shi K, Vaupel P. Intra- and intertumor heterogeneities in total, chronic, and acute hypoxia in xenografted squamous cell carcinomas. Detection and quantification using (immuno-)fluorescence techniques. *Strahlenther Onkol* 2012; 188: 606-15.

32. McCall KC, Humm JL, Bartlett R, Reese M, Carlin S. Copper-64-diacetyl-bis(N(4)-methylthiosemicarbazone) Pharmacokinetics in FaDu Xenograft Tumors and Correlation With Microscopic Markers of Hypoxia. *Int J Radiat Oncol Biol Phys* 2012; 84: e393-9.
33. Saito K, Matsumoto S, Devasahayam N, et al. Transient decrease in tumor oxygenation after intravenous administration of pyruvate. *Magn Reson Med* 2012; 67: 801-7.