

# APPLICATIONS OF HYPOXYPROBE™-1 IN NORMAL AND TUMOR TISSUES

## CELL CULTURE

1. Chou, S. C., Flood, P. M., and Raleigh, J. A. Marking hypoxic cells for complement and cytotoxic T lymphocyte-mediated lysis: using pimonidazole. *Br J Cancer Suppl*, 27: S213-216, 1996.
2. Cowan, D. S., Hicks, K. O., and Wilson, W. R. Multicellular membranes as an in vitro model for extravascular diffusion in tumours. *Br J Cancer Suppl*, 27: S28-31, 1996.
3. Sminia, P., Acker, H., Eikesdal, H. P., Kaaijk, P., Enger, P., Slotman, B., and Bjerkvig, R. Oxygenation and response to irradiation of organotypic multicellular spheroids of human glioma. *Anticancer Res.*, 23: 1461-1466, 2003.
4. Prabhakaran, K., Sampson, D. A., and Hoehner, J. C. Neuroblastoma survival and death: an in vitro model of hypoxia and metabolic stress. *J. Surg. Res.*, 116: 288-296, 2004.
5. Hofer, S. O., Mitchell, G. M., Penington, A. J., Morrison, W. A., Romeomeeuw, R., Keramidaris, E., Palmer, J., and Knight, K. R. The use of pimonidazole to characterise hypoxia in the internal environment of an in vivo tissue engineering chamber. *Br J Plast Surg*, 2005.
6. Kempf, V. A., Lebidziejewski, M., Alitalo, K., Walzlein, J. H., Eehalt, U., Fiebig, J., Huber, S., Schutt, B., Sander, C. A., Muller, S., Grassl, G., Yazdi, A. S., Brehm, B., and Autenrieth, I. B. Activation of hypoxia-inducible factor-1 in bacillary angiomatosis: evidence for a role of hypoxia-inducible factor-1 in bacterial infections. *Circulation*, 111: 1054-1062, 2005.
7. Kleiter, M. M., Thrall, D. E., Malarkey, D. E., Ji, X., Lee, D. Y., Chou, S. C., and Raleigh, J. A. 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*, 64: 592-602, 2006.

## NORMAL TISSUE - EXPERIMENTAL

### *Bladder*

1. Ghafar, M. A., Anastasiadis, A. G., Olsson, L. E., Chichester, P., Kaplan, S. A., Buttyan, R., and Levin, R. M. Hypoxia and an angiogenic response in the partially obstructed rat bladder. *Lab Invest*, 82: 903-909, 2002.

2. Ghafar, M. A., Shabsigh, A., Chichester, P., Anastasiadis, A. G., Borow, A., Levin, R. M., and Buttyan, R. Effects of chronic partial outlet obstruction on blood flow and oxygenation of the rat bladder. *J Urol*, *167*: 1508-1512, 2002.
3. Levin, R. M., O'Connor, L. J., Leggett, R. E., Whitbeck, C., and Chichester, P. Focal hypoxia of the obstructed rabbit bladder wall correlates with intermediate decompensation. *Neurourol Urodyn*, *22*: 156-163, 2003.
4. Damaser, M. S., Whitbeck, C., Chichester, P., and Levin, R. M. Effect of vaginal distension on blood flow and hypoxia of urogenital organs of the female rat. *J Appl Physiol*, *98*: 1884-1890, 2005.
5. Badger, W. J., Whitbeck, C., Kogan, B., Chichester, P., and Levin, R. M. The immediate effect of castration on female rabbit bladder blood flow and tissue oxygenation. *Urol Int*, *76*: 264-268, 2006.

### ***Bone***

1. Dodd, J. S., Raleigh, J. A., and Gross, T. S. Osteocyte hypoxia: a novel mechanotransduction pathway. *Am. J. Physiol. Renal. Physiol.*, *277*: C598-602, 1999.
2. Asosingh, K., De Raeve, H., de Ridder, M., Storme, G. A., Willems, A., Van Riet, I., Van Camp, B., and Vanderkerken, K. Role of the hypoxic bone marrow microenvironment in 5T2MM murine myeloma tumor progression. *Haematologica*, *90*: 810-817, 2005.
3. Villanueva, S., Cespedes, C., and Vio, C. P. Ischemic acute renal failure induces the expression of a wide range of nephrogenic proteins. *Am J Physiol Regul Integr Comp Physiol*, *290*: R861-870, 2006.

### ***Brain***

1. Forder, J. P., Munzenmaier, D. H., and Greene, A. S. Angiogenic protection from focal ischemia with angiotensin II type 1 receptor blockade in the rat. *Am J Physiol Heart Circ Physiol*, *288*: H1989-1996, 2005.
2. Morani, A., Barros, R. P., Imamov, O., Hultenby, K., Arner, A., Warner, M., and Gustafsson, J. A. Lung dysfunction causes systemic hypoxia in estrogen receptor beta knockout (ERbeta<sup>-/-</sup>) mice. *Proc Natl Acad Sci U S A*, *103*: 7165-7169, 2006.
3. Nanka, O., Valasek, P., Dvorakova, M., and Grim, M. Experimental hypoxia and embryonic angiogenesis. *Dev Dyn*, *235*: 723-733, 2006.

### ***Embryo***

1. Lee, Y. M., Jeong, C. H., Koo, S. Y., Son, M. J., Song, H. S., Bae, S. K., Raleigh, J. A., Chung, H. Y., Yoo, M. A., and Kim, K. W. Determination of hypoxic region by hypoxia marker in developing mouse embryos in vivo: a possible signal for vessel development. *Dev. Dyn.*, *220*: 175-186, 2001.

2. Bassnett, S. and McNulty, R. The effect of elevated intraocular oxygen on organelle degradation in the embryonic chicken lens. *J. Exp. Biol.*, 206: 4353-4361, 2003.
3. Danielsson, B. R., Skold, A. C., Johansson, A., Dillner, B., and Blomgren, B. Teratogenicity by the hERG potassium channel blocking drug almokalant: use of hypoxia marker gives evidence for a hypoxia-related mechanism mediated via embryonic arrhythmia. *Toxicol. Appl. Pharmacol.*, 193: 168-176, 2003.
4. Freeburg, P. B., Robert, B., St John, P. L., and Abrahamson, D. R. Podocyte expression of hypoxia-inducible factor (HIF)-1 and HIF-2 during glomerular development. *J Am Soc Nephrol*, 14: 927-938, 2003.
5. Danielsson, B. R., Johansson, A., Danielsson, C., Azarbayjani, F., Blomgren, B., and Skold, A. C. Phenytoin teratogenicity: Hypoxia marker and effects on embryonic heart rhythm suggest an hERG-related mechanism. *Birth Defects Res A Clin Mol Teratol*, 73: 146-153, 2005.
6. Freeburg, P. B. and Abrahamson, D. R. Divergent expression patterns for hypoxia-inducible factor-1beta and aryl hydrocarbon receptor nuclear transporter-2 in developing kidney. *J Am Soc Nephrol*, 15: 2569-2578, 2004.
7. Nanka, O., Valasek, P., Dvorakova, M., and Grim, M. Experimental hypoxia and embryonic angiogenesis. *Dev Dyn*, 235: 723-733, 2006.

### *Eye*

1. Cobb, L. M., Nolan, J., and Butler, S. A. Distribution of pimonidazole and RSU 1069 in tumour and normal tissues. *Br J Cancer*, 62: 915-918, 1990.
2. Gardiner, T. A., Gibson, D. S., de Gooyer, T. E., de la Cruz, V. F., McDonald, D. M., and Stitt, A. W. Inhibition of Tumor Necrosis Factor- $\alpha$  Improves Physiological Angiogenesis and Reduces Pathological Neovascularization in Ischemic Retinopathy. *Am. J. Pathol.*, 166: 637-644, 2005.
3. Danylkova, N. O., Pomeranz, H. D., Alcalá, S. R., and McLoon, L. K. Histological and morphometric evaluation of transient retinal and optic nerve ischemia in rat. *Brain Res*, 1096: 20-29, 2006.

### *Heart*

1. Sinusas, A. J. The potential for myocardial imaging with hypoxia markers. *Semin Nucl Med*, 29: 330-338, 1999.
2. Lee, Y. M., Jeong, C. H., Koo, S. Y., Son, M. J., Song, H. S., Bae, S. K., Raleigh, J. A., Chung, H. Y., Yoo, M. A., and Kim, K. W. Determination of hypoxic region by hypoxia marker in developing mouse embryos in vivo: a possible signal for vessel development. *Dev. Dyn.*, 220: 175-186, 2001.
3. Danielsson, B. R., Skold, A. C., Johansson, A., Dillner, B., and Blomgren, B. Teratogenicity by the hERG potassium channel blocking drug almokalant: use of hypoxia marker gives evidence for a hypoxia-related mechanism mediated via embryonic arrhythmia. *Toxicol. Appl. Pharmacol.*, 193: 168-176, 2003.
4. Danielsson, B. R., Johansson, A., Danielsson, C., Azarbayjani, F., Blomgren, B., and Skold, A. C. Phenytoin teratogenicity: Hypoxia marker and effects on

- embryonic heart rhythm suggest an hERG-related mechanism. *Birth Defects Res A Clin Mol Teratol*, 73: 146-153, 2005.
5. Cheema, A. N., Hong, T., Nili, N., Segev, A., Moffat, J. G., Lipson, K. E., Howlett, A. R., Holdsworth, D. W., Cole, M. J., Qiang, B., Kolodgie, F., Virmani, R., Stewart, D. J., and Strauss, B. H. Adventitial microvessel formation after coronary stenting and the effects of SU11218, a tyrosine kinase inhibitor. *J Am Coll Cardiol*, 47: 1067-1075, 2006.
  6. Morani, A., Barros, R. P., Imamov, O., Hultenby, K., Arner, A., Warner, M., and Gustafsson, J. A. Lung dysfunction causes systemic hypoxia in estrogen receptor beta knockout (ERbeta<sup>-/-</sup>) mice. *Proc Natl Acad Sci U S A*, 103: 7165-7169, 2006.

### ***Inflammatory cells***

1. Arteel, G. E., Iimuro, Y., Yin, M., Raleigh, J. A., and Thurman, R. G. Chronic enteral ethanol treatment causes hypoxia in rat liver tissue in vivo. *Hepatology*, 25: 920-926, 1997.
2. Thurman, R. G. II. Alcoholic liver injury involves activation of Kupffer cells by endotoxin. *Am J Physiol*, 275: G605-611, 1998.
3. Thurman, R. G., Bradford, B. U., Iimuro, Y., Knecht, K. T., Arteel, G. E., Yin, M., Connor, H. D., Wall, C., Raleigh, J. A., Frankenberg, M. V., Adachi, Y., Forman, D. T., Brenner, D., Kadiiska, M., and Mason, R. P. The role of gut-derived bacterial toxins and free radicals in alcohol-induced liver injury. *J Gastroenterol Hepatol*, 13 Suppl: S39-50, 1998.
4. Thurman, R. G. Sex-related liver injury due to alcohol involves activation of Kupffer cells by endotoxin. *Can J Gastroenterol*, 14 Suppl D: 129D-135D, 2000.
5. Albina, J. E., Mastrofrancesco, B., Vessella, J. A., Louis, C. A., Henry, W. L., Jr., and Reichner, J. S. HIF-1 expression in healing wounds: HIF-1alpha induction in primary inflammatory cells by TNF-alpha. *Am J Physiol Cell Physiol*, 281: C1971-1977, 2001.
6. Peters, C. L., Morris, C. J., Mapp, P. I., Blake, D. R., Lewis, C. E., and Winrow, V. R. The transcription factors hypoxia-inducible factor 1alpha and Ets-1 colocalize in the hypoxic synovium of inflamed joints in adjuvant-induced arthritis. *Arthritis Rheum.*, 50: 291-296, 2004.
7. Lewis, C. and Murdoch, C. Macrophage responses to hypoxia: implications for tumor progression and anti-cancer therapies. *Am J Pathol*, 167: 627-635, 2005.
8. Murdoch, C. and Lewis, C. E. Macrophage migration and gene expression in response to tumor hypoxia. *Int J Cancer*, 117: 701-708, 2005.

### ***Kidney***

1. Cobb, L. M., Nolan, J., and Butler, S. A. Distribution of pimonidazole and RSU 1069 in tumour and normal tissues. *Br J Cancer*, 62: 915-918, 1990.
2. Zhong, Z., Arteel, G. E., Connor, H. D., Yin, M., Frankenberg, M. V., Stachlewitz, R. F., Raleigh, J. A., Mason, R. P., and Thurman, R. G. Cyclosporin

- A increases hypoxia and free radical production in rat kidneys: prevention by dietary glycine. *Am J Physiol*, 275: F595-604, 1998.
3. Suga, S. I., Phillips, M. I., Ray, P. E., Raleigh, J. A., Vio, C. P., Kim, Y. G., Mazzali, M., Gordon, K. L., Hughes, J., and Johnson, R. J. Hypokalemia induces renal injury and alterations in vasoactive mediators that favor salt sensitivity. *Am. J. Physiol. Renal. Physiol.*, 281: F620-629, 2001.
  4. Basile, D. P., Donohoe, D. L., Roethe, K., and Mattson, D. L. Chronic renal hypoxia after acute ischemic injury: effects of L-arginine on hypoxia and secondary damage. *Am J Physiol Renal Physiol*, 284: F338-348, 2003.
  5. Cachat, F., Lange-Sperandio, B., Chang, A. Y., Kiley, S. C., Thornhill, B. A., Forbes, M. S., and Chevalier, R. L. Ureteral obstruction in neonatal mice elicits segment-specific tubular cell responses leading to nephron loss. *Kidney Int*, 63: 564-575, 2003.
  6. Freeburg, P. B., Robert, B., St John, P. L., and Abrahamson, D. R. Podocyte expression of hypoxia-inducible factor (HIF)-1 and HIF-2 during glomerular development. *J Am Soc Nephrol*, 14: 927-938, 2003.
  7. Freeburg, P. B. and Abrahamson, D. R. Divergent expression patterns for hypoxia-inducible factor-1beta and aryl hydrocarbon receptor nuclear transporter-2 in developing kidney. *J Am Soc Nephrol*, 15: 2569-2578, 2004.
  8. Manotham, K., Tanaka, T., Matsumoto, M., Ohse, T., Miyata, T., Inagi, R., Kurokawa, K., Fujita, T., and Nangaku, M. Evidence of tubular hypoxia in the early phase in the remnant kidney model. *J. Am. Soc. Nephrol.*, 15: 1277-1288, 2004.
  9. van Wijngaarden, J., de Rooij, K., van Beek, E., Bernsen, H., Que, I., van Hinsbergh, V. W., and Lowik, C. Identification of differentially expressed genes in a renal cell carcinoma tumor model after endostatin-treatment. *Lab Invest*, 84: 1472-1483, 2004.
  10. Covington, M. D., Bayless, K. J., Burghardt, R. C., Davis, G. E., and Parrish, A. R. Ischemia-induced cleavage of cadherins in NRK cells: evidence for a role of metalloproteinases. *Am J Physiol Renal Physiol*, 289: F280-288, 2005.
  11. Rosenberger, C., Heyman, S. N., Rosen, S., Shina, A., Goldfarb, M., Griethe, W., Frei, U., Reinke, P., Bachmann, S., and Eckardt, K. U. Up-regulation of HIF in experimental acute renal failure: Evidence for a protective transcriptional response to hypoxia. *Kidney Int*, 67: 531-542, 2005.
  12. Wang, P. X. and Sanders, P. W. Mechanism of hypertensive nephropathy in the Dahl/Rapp rat: a primary disorder of vascular smooth muscle. *Am J Physiol Renal Physiol*, 288: F236-242, 2005.
  13. Goldfarb, M., Rosenberger, C., Abassi, Z., Shina, A., Zilbersat, F., Eckardt, K. U., Rosen, S., and Heyman, S. N. Acute-on-chronic renal failure in the rat: functional compensation and hypoxia tolerance. *Am J Nephrol*, 26: 22-33, 2006.
  14. Morani, A., Barros, R. P., Imamov, O., Hultenby, K., Arner, A., Warner, M., and Gustafsson, J. A. Lung dysfunction causes systemic hypoxia in estrogen receptor beta knockout (ERbeta<sup>-/-</sup>) mice. *Proc Natl Acad Sci U S A*, 103: 7165-7169, 2006.
  15. Nanka, O., Valasek, P., Dvorakova, M., and Grim, M. Experimental hypoxia and embryonic angiogenesis. *Dev Dyn*, 235: 723-733, 2006.

16. Villanueva, S., Cespedes, C., and Vio, C. P. Ischemic acute renal failure induces the expression of a wide range of nephrogenic proteins. *Am J Physiol Regul Integr Comp Physiol*, 290: R861-870, 2006.

### *Liver*

1. Cobb, L. M., Nolan, J., and Butler, S. A. Distribution of pimonidazole and RSU 1069 in tumour and normal tissues. *Br J Cancer*, 62: 915-918, 1990.
2. Arteel, G. E., Thurman, R. G., Yates, J. M., and Raleigh, J. A. Evidence that hypoxia markers detect oxygen gradients in liver: pimonidazole and retrograde perfusion of rat liver. *Br J Cancer*, 72: 889-895, 1995.
3. Arteel, G. E., Raleigh, J. A., Bradford, B. U., and Thurman, R. G. Acute alcohol produces hypoxia directly in rat liver tissue in vivo: role of Kupffer cells. *Am J Physiol*, 271: G494-500, 1996.
4. Arteel, G. E., Iimuro, Y., Yin, M., Raleigh, J. A., and Thurman, R. G. Chronic enteral ethanol treatment causes hypoxia in rat liver tissue in vivo. *Hepatology*, 25: 920-926, 1997.
5. Stachlewitz, R. F., Arteel, G. E., Raleigh, J. A., Connor, H. D., Mason, R. P., and Thurman, R. G. Development and characterization of a new model of tacrine-induced hepatotoxicity: role of the sympathetic nervous system and hypoxia-reoxygenation. *J Pharmacol Exp Ther*, 282: 1591-1599, 1997.
6. Arteel, G. E., Thurman, R. G., and Raleigh, J. A. Reductive metabolism of the hypoxia marker pimonidazole is regulated by oxygen tension independent of the pyridine nucleotide redox state. *Eur J Biochem*, 253: 743-750, 1998.
7. Thurman, R. G. II. Alcoholic liver injury involves activation of Kupffer cells by endotoxin. *Am J Physiol*, 275: G605-611, 1998.
8. Thurman, R. G., Bradford, B. U., Iimuro, Y., Knecht, K. T., Arteel, G. E., Yin, M., Connor, H. D., Wall, C., Raleigh, J. A., Frankenberg, M. V., Adachi, Y., Forman, D. T., Brenner, D., Kadiiska, M., and Mason, R. P. The role of gut-derived bacterial toxins and free radicals in alcohol-induced liver injury. *J Gastroenterol Hepatol*, 13 Suppl: S39-50, 1998.
9. Rosmorduc, O., Wendum, D., Corpechot, C., Galy, B., Sebbagh, N., Raleigh, J., Housset, C., and Poupon, R. Hepatocellular hypoxia-induced vascular endothelial growth factor expression and angiogenesis in experimental biliary cirrhosis. *Am J Pathol*, 155: 1065-1073, 1999.
10. Schemmer, P., Bradford, B. U., Rose, M. L., Bunzendahl, H., Raleigh, J. A., Lemasters, J. J., and Thurman, R. G. Intravenous glycine improves survival in rat liver transplantation. *Am J Physiol*, 276: G924-932, 1999.
11. Schemmer, P., Bunzendahl, H., Raleigh, J. A., and Thurman, R. G. Graft survival is improved by hepatic denervation before organ harvesting. *Transplantation*, 67: 1301-1307, 1999.
12. Schemmer, P., Connor, H. D., Arteel, G. E., Raleigh, J. A., Bunzendahl, H., Mason, R. P., and Thurman, R. G. Reperfusion injury in livers due to gentle in situ organ manipulation during harvest involves hypoxia and free radicals. *J Pharmacol Exp Ther*, 290: 235-240, 1999.

13. Zhong, Z., Arteel, G. E., Connor, H. D., Schemmer, P., Chou, S. C., Raleigh, J. A., Mason, R. P., Lemasters, J. J., and Thurman, R. G. Binge drinking disturbs hepatic microcirculation after transplantation: prevention with free radical scavengers. *J Pharmacol Exp Ther*, *290*: 611-620, 1999.
14. Thurman, R. G. Sex-related liver injury due to alcohol involves activation of Kupffer cells by endotoxin. *Can J Gastroenterol*, *14 Suppl D*: 129D-135D, 2000.
15. Schemmer, P., Enomoto, N., Bradford, B. U., Bunzendahl, H., Raleigh, J. A., Lemasters, J. J., and Thurman, R. G. Activated Kupffer cells cause a hypermetabolic state after gentle in situ manipulation of liver in rats. *Am J Physiol Gastrointest Liver Physiol*, *280*: G1076-1082, 2001.
16. Schemmer, P., Enomoto, N., Bradford, B. U., Bunzendahl, H., Raleigh, J. A., and Thurman, R. G. Autonomic nervous system and gut-derived endotoxin: involvement in activation of kupffer cells after in situ organ manipulation. *World J Surg*, *25*: 399-406, 2001.
17. Zhong, Z., Li, X., Yamashina, S., von Frankenberg, M., Enomoto, N., Ikejima, K., Kolinsky, M., Raleigh, J. A., and Thurman, R. G. Cyclosporin A causes a hypermetabolic state and hypoxia in the liver: prevention by dietary glycine. *J Pharmacol Exp Ther*, *299*: 858-865, 2001.
18. Bardag-Gorce, F., French, B. A., Li, J., Riley, N. E., Yuan, Q. X., Valinluck, V., Fu, P., Ingelman-Sundberg, M., Yoon, S., and French, S. W. The importance of cycling of blood alcohol levels in the pathogenesis of experimental alcoholic liver disease in rats. *Gastroenterology*, *123*: 325-335, 2002.
19. Corpechot, C., Barbu, V., Wendum, D., Chignard, N., Housset, C., Poupon, R., and Rosmorduc, O. Hepatocyte growth factor and c-Met inhibition by hepatic cell hypoxia: a potential mechanism for liver regeneration failure in experimental cirrhosis. *Am J Pathol*, *160*: 613-620, 2002.
20. McKim, S. E., Uesugi, T., Raleigh, J. A., McClain, C. J., and Arteel, G. E. Chronic intragastric alcohol exposure causes hypoxia and oxidative stress in the rat pancreas. *Arch Biochem Biophys*, *417*: 34-43, 2003.
21. Cople, B. L., Rondelli, C. M., Maddox, J. F., Hoglen, N. C., Ganey, P. E., and Roth, R. A. Modes of cell death in rat liver after monocrotaline exposure. *Toxicol Sci*, *77*: 172-182, 2004.
22. Jeong, W. I., Do, S. H., Yun, H. S., Song, B. J., Kim, S. J., Kwak, W. J., Yoo, S. E., Park, H. Y., and Jeong, K. S. Hypoxia potentiates transforming growth factor-beta expression of hepatocyte during the cirrhotic condition in rat liver. *Liver Int*, *24*: 658-668, 2004.
23. Morani, A., Barros, R. P., Imamov, O., Hultenby, K., Arner, A., Warner, M., and Gustafsson, J. A. Lung dysfunction causes systemic hypoxia in estrogen receptor beta knockout (ERbeta<sup>-/-</sup>) mice. *Proc Natl Acad Sci U S A*, *103*: 7165-7169, 2006.

## ***Ovary***

1. Morani, A., Barros, R. P., Imamov, O., Hultenby, K., Arner, A., Warner, M., and Gustafsson, J. A. Lung dysfunction causes systemic hypoxia in estrogen receptor

beta knockout (ERbeta<sup>-/-</sup>) mice. *Proc Natl Acad Sci U S A*, *103*: 7165-7169, 2006.

### ***Pancreas***

1. McKim, S. E., Uesugi, T., Raleigh, J. A., McClain, C. J., and Arteel, G. E. Chronic intragastric alcohol exposure causes hypoxia and oxidative stress in the rat pancreas. *Arch Biochem Biophys*, *417*: 34-43, 2003.

### ***Prostate***

1. Shabsigh, A., Ghafar, M. A., de la Taille, A., Burchardt, M., Kaplan, S. A., Anastasiadis, A. G., and Buttyan, R. Biomarker analysis demonstrates a hypoxic environment in the castrated rat ventral prostate gland. *J Cell Biochem*, *81*: 437-444, 2001.
2. Morani, A., Barros, R. P., Imamov, O., Hultenby, K., Arner, A., Warner, M., and Gustafsson, J. A. Lung dysfunction causes systemic hypoxia in estrogen receptor beta knockout (ERbeta<sup>-/-</sup>) mice. *Proc Natl Acad Sci U S A*, *103*: 7165-7169, 2006.

### ***Skin***

1. Cobb, L. M., Nolan, J., and Butler, S. A. Distribution of pimonidazole and RSU 1069 in tumour and normal tissues. *Br J Cancer*, *62*: 915-918, 1990.
2. Haroon, Z. A., Raleigh, J. A., Greenberg, C. S., and Dewhirst, M. W. Early wound healing exhibits cytokine surge without evidence of hypoxia. *Ann Surg*, *231*: 137-147, 2000.
3. Albina, J. E., Mastrofrancesco, B., Vessella, J. A., Louis, C. A., Henry, W. L., Jr., and Reichner, J. S. HIF-1 expression in healing wounds: HIF-1alpha induction in primary inflammatory cells by TNF-alpha. *Am J Physiol Cell Physiol*, *281*: C1971-1977, 2001.

### ***Thymus***

1. Hale, L. P., Braun, R. D., Gwinn, W. M., Greer, P. K., and Dewhirst, M. W. Hypoxia in the thymus: role of oxygen tension in thymocyte survival. *Am J Physiol Heart Circ Physiol*, *282*: H1467-1477, 2002.

### ***Urethra***

1. Damaser, M. S., Whitbeck, C., Chichester, P., and Levin, R. M. Effect of vaginal distension on blood flow and hypoxia of urogenital organs of the female rat. *J Appl Physiol*, *98*: 1884-1890, 2005.

### ***Vagina***



1. Damaser, M. S., Whitbeck, C., Chichester, P., and Levin, R. M. Effect of vaginal distension on blood flow and hypoxia of urogenital organs of the female rat. *J Appl Physiol*, 98: 1884-1890, 2005.

### ***Wounds***

1. Haroon, Z. A., Raleigh, J. A., Greenberg, C. S., and Dewhirst, M. W. Early wound healing exhibits cytokine surge without evidence of hypoxia. *Ann Surg*, 231: 137-147, 2000.
2. Albina, J. E., Mastrofrancesco, B., Vessella, J. A., Louis, C. A., Henry, W. L., Jr., and Reichner, J. S. HIF-1 expression in healing wounds: HIF-1alpha induction in primary inflammatory cells by TNF-alpha. *Am J Physiol Cell Physiol*, 281: C1971-1977, 2001.
3. Lokmic, Z., Darby, I. A., Thompson, E. W., and Mitchell, G. M. Time course analysis of hypoxia, granulation tissue and blood vessel growth, and remodeling in healing rat cutaneous incisional primary intention wounds. *Wound Repair Regen*, 14: 277-288, 2006.

## **CANCER– EXPERIMENTAL**

### ***Brain***

1. Bernsen, H. J., Rijken, P. F., Peters, J. P., Bakker, J. H., Boerman, R. H., Wesseling, P., and van der Kogel, A. J. Suramin treatment of human glioma xenografts; effects on tumor vasculature and oxygenation status. *J Neurooncol*, 44: 129-136, 1999.
2. Bernsen, H. J., Rijken, P. F., Peters, H., Raleigh, J. A., Jeuken, J. W., Wesseling, P., and van der Kogel, A. J. Hypoxia in a human intracerebral glioma model. *J Neurosurg*, 93: 449-454, 2000.
3. Olive, P. L., Durand, R. E., Raleigh, J. A., Luo, C., and Aquino-Parsons, C. Comparison between the comet assay and pimonidazole binding for measuring tumour hypoxia. *Br J Cancer*, 83: 1525-1531, 2000.
4. Wijffels, K. I., Kaanders, J. H., Rijken, P. F., Bussink, J., van den Hoogen, F. J., Marres, H. A., de Wilde, P. C., Raleigh, J. A., and van der Kogel, A. J. Vascular architecture and hypoxic profiles in human head and neck squamous cell carcinomas. *Br J Cancer*, 83: 674-683, 2000.
5. Eikesdal, H. P., Bjerkvig, R., Raleigh, J. A., Mella, O., and Dahl, O. Tumor vasculature is targeted by the combination of combretastatin A-4 and hyperthermia. *Radiother Oncol*, 61: 313-320, 2001.
6. Hoebbers, F. J., Janssen, H. L., Olmos, A. V., Sprong, D., Nunn, A. D., Balm, A. J., Hoefnagel, C. A., Begg, A. C., Haustermans, K. M., Ljungkvist, A. S., Bussink, J., Rijken, P. F., Kaanders, J. H., van der Kogel, A. J., Denekamp, J., and Bonn, D. Phase 1 study to identify tumour hypoxia in patients with head and neck cancer using technetium-99m BRU 59-21. Vascular architecture, hypoxia, and

- proliferation in first-generation xenografts of human head-and-neck squamous cell carcinomas. Why do hypoxic cells behave badly? *Eur J Nucl Med Mol Imaging*, *29*: 1206-1211, 2002.
7. Sminia, P., Acker, H., Eikesdal, H. P., Kaaijk, P., Enger, P., Slotman, B., and Bjerkgvig, R. Oxygenation and response to irradiation of organotypic multicellular spheroids of human glioma. *Anticancer Res.*, *23*: 1461-1466, 2003.
  8. Zoula, S., Rijken, P. F., Peters, J. P., Farion, R., Van der Sanden, B. P., Van der Kogel, A. J., Decorps, M., and Remy, C. Pimonidazole binding in C6 rat brain glioma: relation with lipid droplet detection. *Br J Cancer*, *88*: 1439-1444, 2003.
  9. Cardenas-Navia, L. I., Yu, D., Braun, R. D., Brizel, D. M., Secomb, T. W., and Dewhirst, M. W. Tumor-dependent kinetics of partial pressure of oxygen fluctuations during air and oxygen breathing. *Cancer Res*, *64*: 6010-6017, 2004.
  10. Kostourou, V., Troy, H., Murray, J. F., Cullis, E. R., Whitley, G. S., Griffiths, J. R., and Robinson, S. P. Overexpression of dimethylarginine dimethylaminohydrolase enhances tumor hypoxia: an insight into the relationship of hypoxia and angiogenesis in vivo. *Neoplasia*, *6*: 401-411, 2004.
  11. Schuurung, J., Bussink, J., Bernsen, H. J., Peeters, W., and van Der Kogel, A. J. Irradiation combined with SU5416: microvascular changes and growth delay in a human xenograft glioblastoma tumor line. *Int J Radiat Oncol Biol Phys*, *61*: 529-534, 2005.
  12. Sobhanifar, S., Aquino-Parsons, C., Stanbridge, E. J., and Olive, P. Reduced Expression of Hypoxia-Inducible Factor-1{alpha} in Perinecrotic Regions of Solid Tumors. *Cancer Res*, *65*: 7259-7266, 2005.
  13. Yuan, H., Schroeder, T., Bowsher, J. E., Hedlund, L. W., Wong, T., and Dewhirst, M. W. Intertumoral differences in hypoxia selectivity of the PET imaging agent <sup>64</sup>Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone). *J Nucl Med*, *47*: 989-998, 2006.

### ***Breast***

1. Raleigh, J. A., Chou, S. C., Tables, L., Suchindran, S., Varia, M. A., and Horsman, M. R. Relationship of hypoxia to metallothionein expression in murine tumors. *Int J Radiat Oncol Biol Phys*, *42*: 727-730, 1998.
2. Raleigh, J. A., Chou, S. C., Arteel, G. E., and Horsman, M. R. Comparisons among pimonidazole binding, oxygen electrode measurements, and radiation response in C3H mouse tumors. *Radiat Res*, *151*: 580-589, 1999.
3. Samoszuk, M. and Corwin, M. A. Mast cell inhibitor cromolyn increases blood clotting and hypoxia in murine breast cancer. *Int J Cancer*, *107*: 159-163, 2003.
4. Cao, Y., Li, C. Y., Moeller, B. J., Yu, D., Zhao, Y., Dreher, M. R., Shan, S., and Dewhirst, M. W. Observation of incipient tumor angiogenesis that is independent of hypoxia and hypoxia inducible factor-1 activation. *Cancer Res*, *65*: 5498-5505, 2005.
5. Lipnik, K., Greco, O., Scott, S., Knapp, E., Mayrhofer, E., Rosenfellner, D., Gunzburg, W. H., Salmons, B., and Hohenadl, C. Hypoxia- and radiation-inducible, breast cell-specific targeting of retroviral vectors. *Virology*, *349*: 121-133, 2006.

6. Franco, M., Man, S., Chen, L., Emmenegger, U., Shaked, Y., Cheung, A. M., Brown, A. S., Hicklin, D. J., Foster, F. S., and Kerbel, R. S. 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*, *66*: 3639-3648, 2006.
7. Kirkpatrick, J. P., Hardee, M. E., Snyder, S. A., Peltz, C. M., Zhao, Y., Brizel, D. M., Dewhirst, M. W., and Blackwell, K. L. The effect of darbepoetin alfa on growth, oxygenation and radioresponsiveness of a breast adenocarcinoma. *Radiat Res*, *165*: 192-201, 2006.
8. Yuan, H., Schroeder, T., Bowsher, J. E., Hedlund, L. W., Wong, T., and Dewhirst, M. W. Intertumoral differences in hypoxia selectivity of the PET imaging agent <sup>64</sup>Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone). *J Nucl Med*, *47*: 989-998, 2006.

### ***Colorectal***

1. van Laarhoven, H. W., Bussink, J., Lok, J., Punt, C. J., Heerschap, A., and van Der Kogel, A. J. Effects of nicotinamide and carbogen in different murine colon carcinomas: immunohistochemical analysis of vascular architecture and microenvironmental parameters. *Int J Radiat Oncol Biol Phys*, *60*: 310-321, 2004.
2. Huxham, L. A., Kyle, A. H., Baker, J. H., Nykilchuk, L. K., and Minchinton, A. I. Microregional effects of gemcitabine in HCT-116 xenografts. *Cancer Res*, *64*: 6537-6541, 2004.
3. Cao, Y., Li, C. Y., Moeller, B. J., Yu, D., Zhao, Y., Dreher, M. R., Shan, S., and Dewhirst, M. W. Observation of incipient tumor angiogenesis that is independent of hypoxia and hypoxia inducible factor-1 activation. *Cancer Res*, *65*: 5498-5505, 2005.
4. Ljungkvist, A. S., Bussink, J., Kaanders, J. H., Rijken, P. F., Begg, A. C., Raleigh, J. A., and van der Kogel, A. J. Hypoxic cell turnover in different solid tumor lines. *Int J Radiat Oncol Biol Phys*, *62*: 1157-1168, 2005.
5. Sobhanifar, S., Aquino-Parsons, C., Stanbridge, E. J., and Olive, P. Reduced Expression of Hypoxia-Inducible Factor-1{alpha} in Perinecrotic Regions of Solid Tumors. *Cancer Res*, *65*: 7259-7266, 2005.
6. Mizukami, Y., Jo, W. S., Duerr, E. M., Gala, M., Li, J., Zhang, X., Zimmer, M. A., Iliopoulos, O., Zukerberg, L. R., Kohgo, Y., Lynch, M. P., Rueda, B. R., and Chung, D. C. Induction of interleukin-8 preserves the angiogenic response in HIF-1alpha-deficient colon cancer cells. *Nat Med*, *11*: 992-997, 2005.

### ***Kidney***

1. van Wijngaarden, J., de Rooij, K., van Beek, E., Bernsen, H., Que, I., van Hinsbergh, V. W., and Lowik, C. Identification of differentially expressed genes in a renal cell carcinoma tumor model after endostatin-treatment. *Lab Invest*, *84*: 1472-1483, 2004.

### ***Liver***

1. van Laarhoven, H. W., de Geus-Oei, L. F., Wiering, B., Lok, J., Rijpkema, M., Kaanders, J. H., Krabbe, P. F., Ruers, T., Punt, C. J., van der Kogel, A. J., Oyen, W. J., and Heerschap, A. Gadopentetate dimeglumine and FDG uptake in liver metastases of colorectal carcinoma as determined with MR imaging and PET. *Radiology*, *237*: 181-188, 2005.
2. van Laarhoven, H. W., Kaanders, J. H., Lok, J., Peeters, W. J., Rijken, P. F., Wiering, B., Ruers, T. J., Punt, C. J., Heerschap, A., and van der Kogel, A. J. Hypoxia in relation to vasculature and proliferation in liver metastases in patients with colorectal cancer. *Int J Radiat Oncol Biol Phys*, *64*: 473-482, 2006.

### ***Lung***

1. Rofstad, E. K. and Halsor, E. F. Hypoxia-associated spontaneous pulmonary metastasis in human melanoma xenografts: involvement of microvascular hot spots induced in hypoxic foci by interleukin 8. *Br J Cancer*, *86*: 301-308, 2002.
2. Rofstad, E. K., Tunheim, S. H., Mathiesen, B., Graff, B. A., Halsor, E. F., Nilsen, K., and Galappathi, K. Pulmonary and lymph node metastasis is associated with primary tumor interstitial fluid pressure in human melanoma xenografts. *Cancer Res*, *62*: 661-664, 2002.
3. Rofstad, E. K., Mathiesen, B., and 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.*, *64*: 13-18, 2004.
4. Rofstad, E. K., Mathiesen, B., Henriksen, K., Kindem, K., and Galappathi, K. The Tumor Bed Effect: increased metastatic dissemination from hypoxia-Induced up-regulation of metastasis-promoting gene products. *Cancer Res*, *65*: 2387-2396, 2005.

### ***Melanoma***

1. Lyng, H., Sundfor, K., and Rofstad, E. K. Oxygen tension in human tumours measured with polarographic needle electrodes and its relationship to vascular density, necrosis and hypoxia. *Radiother Oncol*, *44*: 163-169, 1997.
2. Rofstad, E. K. and Maseide, K. Radiobiological and immunohistochemical assessment of hypoxia in human melanoma xenografts: acute and chronic hypoxia in individual tumours. *Int J Radiat Biol*, *75*: 1377-1393, 1999.
3. Danielsen, T. and Rofstad, E. K. 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*, *82*: 1528-1534, 2000.
4. Rofstad, E. K. and Halsor, E. F. Hypoxia-associated spontaneous pulmonary metastasis in human melanoma xenografts: involvement of microvascular hot spots induced in hypoxic foci by interleukin 8. *Br J Cancer*, *86*: 301-308, 2002.

5. Rofstad, E. K., Rasmussen, H., Galappathi, K., Mathiesen, B., Nilsen, K., and Graff, B. A. Hypoxia promotes lymph node metastasis in human melanoma xenografts by up-regulating the urokinase-type plasminogen activator receptor. *Cancer Res.*, *62*: 1847-1853, 2002.
6. Rofstad, E. K., Tunheim, S. H., Mathiesen, B., Graff, B. A., Halsor, E. F., Nilsen, K., and Galappathi, K. Pulmonary and lymph node metastasis is associated with primary tumor interstitial fluid pressure in human melanoma xenografts. *Cancer Res.*, *62*: 661-664, 2002.
7. Rofstad, E. K., Mathiesen, B., and 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.*, *64*: 13-18, 2004.
8. Rofstad, E. K., Mathiesen, B., Henriksen, K., Kindem, K., and Galappathi, K. The Tumor Bed Effect: increased metastatic dissemination from hypoxia-Induced up-regulation of metastasis-promoting gene products. *Cancer Res.*, *65*: 2387-2396, 2005.
9. Liu, J., Qu, R., Ogura, M., Shibata, T., Harada, H., and Hiraoka, M. Real-time Imaging of Hypoxia-inducible Factor-1 Activity in Tumor Xenografts. *J Radiat Res (Tokyo)*, *46*: 93-102, 2005.

### ***Myeloma***

1. Asosingh, K., De Raeve, H., de Ridder, M., Storme, G. A., Willems, A., Van Riet, I., Van Camp, B., and Vanderkerken, K. Role of the hypoxic bone marrow microenvironment in 5T2MM murine myeloma tumor progression. *Haematologica*, *90*: 810-817, 2005.

### ***Prostate***

1. Zhao, D., Ran, S., Constantinescu, A., Hahn, E. W., and Mason, R. P. Tumor oxygen dynamics: correlation of in vivo MRI with histological findings. *Neoplasia*, *5*: 308-318, 2003.
2. O'Donoghue J, A., Zanzonico, P., Pugachev, A., Wen, B., Smith-Jones, P., Cai, S., Burnazi, E., Finn, R. D., Burgman, P., Ruan, S., Lewis, J. S., Welch, M. J., Ling, C. C., and Humm, J. L. 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.*, *61*: 1493-1502, 2005.
3. Pugachev, A., Ruan, S., Carlin, S., Larson, S. M., Campa, J., Ling, C. C., and Humm, J. L. Dependence of FDG uptake on tumor microenvironment. *Int J Radiat Oncol Biol Phys.*, *62*: 545-553, 2005.
4. Durand, R. E. and Raleigh, J. A. Identification of nonproliferating but viable hypoxic tumor cells in vivo. *Cancer Res.*, *58*: 3547-3550, 1998.

## ***Sarcoma***

1. Azuma, C., Raleigh, J. A., and Thrall, D. E. Longevity of pimonidazole adducts in spontaneous canine tumors as an estimate of hypoxic cell lifetime. *Radiat Res*, *148*: 35-42, 1997.
2. Dubois, L., Landuyt, W., Haustermans, K., Dupont, P., Bormans, G., Vermaelen, P., Flamen, P., Verbeken, E., and Mortelmans, L. Evaluation of hypoxia in an experimental rat tumour model by [(18)F]fluoromisonidazole PET and immunohistochemistry. *Br J Cancer*, *91*: 1947-1954, 2004.
3. Kleiter, M. M., Thrall, D. E., Malarkey, D. E., Ji, X., Lee, D. Y., Chou, S. C., and Raleigh, J. A. 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*, *64*: 592-602, 2006.
4. Yuan, H., Schroeder, T., Bowsher, J. E., Hedlund, L. W., Wong, T., and Dewhirst, M. W. Intertumoral differences in hypoxia selectivity of the PET imaging agent <sup>64</sup>Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone). *J Nucl Med*, *47*: 989-998, 2006.

## ***Squamous cell carcinoma***

1. Durand, R. E. and Raleigh, J. A. Identification of nonproliferating but viable hypoxic tumor cells in vivo. *Cancer Res*, *58*: 3547-3550, 1998.
2. Bussink, J., Kaanders, J. H., Rijken, P. F., Raleigh, J. A., and Van der Kogel, A. J. Changes in blood perfusion and hypoxia after irradiation of a human squamous cell carcinoma xenograft tumor line. *Radiat Res*, *153*: 398-404, 2000.
3. Bussink, J., Kaanders, J. H., Strik, A. M., and van der Kogel, A. J. Effects of nicotinamide and carbogen on oxygenation in human tumor xenografts measured with luminescence based fiber-optic probes. *Radiother Oncol*, *57*: 21-30, 2000.
4. Ljungkvist, A. S., Bussink, J., Rijken, P. F., Raleigh, J. A., Denekamp, J., and Van Der Kogel, A. J. Changes in tumor hypoxia measured with a double hypoxic marker technique. *Int J Radiat Oncol Biol Phys*, *48*: 1529-1538, 2000.
5. Olive, P. L., Durand, R. E., Raleigh, J. A., Luo, C., and Aquino-Parsons, C. Comparison between the comet assay and pimonidazole binding for measuring tumour hypoxia. *Br J Cancer*, *83*: 1525-1531, 2000.
6. Lal, A., Peters, H., St Croix, B., Haroon, Z. A., Dewhirst, M. W., Strausberg, R. L., Kaanders, J. H., van der Kogel, A. J., and Riggins, G. J. Transcriptional response to hypoxia in human tumors. *J Natl Cancer Inst*, *93*: 1337-1343, 2001.
7. Zips, D., Eicheler, W., Bruchner, K., Jackisch, T., Geyer, P., Petersen, C., van der Kogel, A. J., and Baumann, M. Impact of the tumour bed effect on microenvironment, radiobiological hypoxia and the outcome of fractionated radiotherapy of human FaDu squamous-cell carcinoma growing in the nude mouse. *Int J Radiat Biol*, *77*: 1185-1193, 2001.
8. Bennewith, K. L., Raleigh, J. A., and Durand, R. E. Orally administered pimonidazole to label hypoxic tumor cells. *Cancer Res*, *62*: 6827-6830, 2002.

9. Olive, P. L., Banath, J. P., and Durand, R. E. The range of oxygenation in SiHa tumor xenografts. *Radiat Res.*, *158*: 159-166, 2002.
10. Petersen, C., Eicheler, W., Frommel, A., Krause, M., Balschukat, S., Zips, D., and Baumann, M. Proliferation and micromilieu during fractionated irradiation of human FaDu squamous cell carcinoma in nude mice. *Int J Radiat Biol*, *79*: 469-477, 2003.
11. O'Donoghue J, A., Zanzonico, P., Pugachev, A., Wen, B., Smith-Jones, P., Cai, S., Burnazi, E., Finn, R. D., Burgman, P., Ruan, S., Lewis, J. S., Welch, M. J., Ling, C. C., and Humm, J. L. 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*, *61*: 1493-1502, 2005.
12. Bennewith, K. L. and Durand, R. E. Quantifying transient hypoxia in human tumor xenografts by flow cytometry. *Cancer Res*, *64*: 6183-6189, 2004.
13. Bhattacharya, A., Toth, K., Mazurchuk, R., Sperryak, J. A., Slocum, H. K., Pendyala, L., Azrak, R., Cao, S., Durrani, F. A., and Rustum, Y. M. 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*, *10*: 8005-8017, 2004.
14. van Herpen, C. M., Bussink, J., van der Kogel, A. J., Peeters, W. J., van der Voort, R., van Schijndel, A., de Wilde, P. C., Adema, G. J., and de Mulder, P. H. 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*, *25*: 1015-10121, 2005.
15. Nelson, D. W., Cao, H., Zhu, Y., Sunar-Reeder, B., Choi, C. Y., Faix, J. D., Brown, J. M., Koong, A. C., Giaccia, A. J., and Le, Q. T. A noninvasive approach for assessing tumor hypoxia in xenografts: developing a urinary marker for hypoxia. *Cancer Res*, *65*: 6151-6158, 2005.
16. Sobhanifar, S., Aquino-Parsons, C., Stanbridge, E. J., and Olive, P. Reduced Expression of Hypoxia-Inducible Factor-1{alpha} in Perinecrotic Regions of Solid Tumors. *Cancer Res*, *65*: 7259-7266, 2005.
17. Solomon, B., Binns, D., Roselt, P., Weibe, L. I., McArthur, G. A., Cullinane, C., and Hicks, R. J. Modulation of intratumoral hypoxia by the epidermal growth factor receptor inhibitor gefitinib detected using small animal PET imaging. *Mol Cancer Ther*, *4*: 1417-1422, 2005.
18. Yaromina, A., Holscher, T., Eicheler, W., Rosner, A., Krause, M., Hessel, F., Petersen, C., Thames, H. D., Baumann, M., and Zips, D. Does heterogeneity of pimonidazole labelling correspond to the heterogeneity of radiation-response of FaDu human squamous cell carcinoma? *Radiother Oncol*, *76*: 206-212, 2005.
19. Ljungkvist, A. S., Bussink, J., Kaanders, J. H., Rijken, P. F., Begg, A. C., Raleigh, J. A., and van der Kogel, A. J. Hypoxic cell turnover in different solid tumor lines. *Int J Radiat Oncol Biol Phys*, *62*: 1157-1168, 2005.

20. Troost, E. G., Bussink, J., Kaanders, J. H., van Eerd, J., Peters, J. P., Rijken, P. F., Boerman, O. C., and van der Kogel, A. J. Comparison of different methods of CAIX quantification in relation to hypoxia in three human head and neck tumor lines. *Radiother Oncol*, 76: 194-199, 2005.
21. Vordermark, D., Kraft, P., Katzer, A., Bolling, T., Willner, J., and Flentje, M. Glucose requirement for hypoxic accumulation of hypoxia-inducible factor-1alpha (HIF-1alpha). *Cancer Lett*, 230: 122-133, 2005.
22. Ljungkvist, A. S., Bussink, J., Kaanders, J. H., Wiedenmann, N. E., Vlasman, R., and van der Kogel, A. J. Dynamics of hypoxia, proliferation and apoptosis after irradiation in a murine tumor model. *Radiat Res*, 165: 326-336, 2006.

## CANCER – CLINICAL

### *Bladder*

1. Wykoff, C. C., Beasley, N. J., Watson, P. H., Turner, K. J., Pastorek, J., Sibtain, A., Wilson, G. D., Turley, H., Talks, K. L., Maxwell, P. H., Pugh, C. W., Ratcliffe, P. J., and Harris, A. L. Hypoxia-inducible expression of tumor-associated carbonic anhydrases. *Cancer Res*, 60: 7075-7083, 2000.
2. Hoskin, P. J., Sibtain, A., Daley, F. M., and Wilson, G. D. GLUT1 and CAIX as intrinsic markers of hypoxia in bladder cancer: relationship with vascularity and proliferation as predictors of outcome of ARCON. *Br J Cancer*, 89: 1290-1297, 2003.
3. Hoskin, P. J., Sibtain, A., Daley, F. M., Saunders, M. I., and Wilson, G. D. The immunohistochemical assessment of hypoxia, vascularity and proliferation in bladder carcinoma. *Radiother Oncol*, 72: 159-168, 2004.

### *Breast*

1. Arcasoy, M. O., Amin, K., Karayal, A. F., Chou, S. C., Raleigh, J. A., Varia, M. A., and Haroon, Z. A. Functional significance of erythropoietin receptor expression in breast cancer. *Lab Invest*, 82: 911-918, 2002.
2. Lewis, C. and Murdoch, C. Macrophage responses to hypoxia: implications for tumor progression and anti-cancer therapies. *Am J Pathol*, 167: 627-635, 2005.
3. Murdoch, C. and Lewis, C. E. Macrophage migration and gene expression in response to tumor hypoxia. *Int J Cancer*, 117: 701-708, 2005.

### *Cervix*

1. Kennedy, A. S., Raleigh, J. A., Perez, G. M., Calkins, D. P., Thrall, D. E., Novotny, D. B., and Varia, M. A. Proliferation and hypoxia in human squamous cell carcinoma of the cervix: first report of combined immunohistochemical assays. *Int J Radiat Oncol Biol Phys*, 37: 897-905, 1997.



2. Raleigh, J. A., Calkins-Adams, D. P., Rinker, L. H., Ballenger, C. A., Weissler, M. C., Fowler, W. C., Jr., Novotny, D. B., and Varia, M. A. Hypoxia and vascular endothelial growth factor expression in human squamous cell carcinomas using pimonidazole as a hypoxia marker. *Cancer Res*, *58*: 3765-3768, 1998.
3. Varia, M. A., Calkins-Adams, D. P., Rinker, L. H., Kennedy, A. S., Novotny, D. B., Fowler, W. C., Jr., and Raleigh, J. A. Pimonidazole: a novel hypoxia marker for complementary study of tumor hypoxia and cell proliferation in cervical carcinoma. *Gynecol Oncol*, *71*: 270-277, 1998.
4. Raleigh, J. A., Chou, S. C., Calkins-Adams, D. P., Ballenger, C. A., Novotny, D. B., and Varia, M. A. A clinical study of hypoxia and metallothionein protein expression in squamous cell carcinomas. *Clin Cancer Res*, *6*: 855-862, 2000.
5. Olive, P. L., Durand, R. E., Raleigh, J. A., Luo, C., and Aquino-Parsons, C. Comparison between the comet assay and pimonidazole binding for measuring tumour hypoxia. *Br J Cancer*, *83*: 1525-1531, 2000.
6. Raleigh, J. A., Chou, S. C., Bono, E. L., Thrall, D. E., and Varia, M. A. Semiquantitative immunohistochemical analysis for hypoxia in human tumors. *Int J Radiat Oncol Biol Phys*, *49*: 569-574, 2001.
7. Raleigh, J. A., Thrall, D. E., and Varia, M. A. Development and clinical application of pimonidazole as a marker for tumor hypoxia. *Recent Res. Devel. Cancer*, *3*: 189-201, 2001.
8. Nordmark, M., Loncaster, J., Chou, S. C., Havsteen, H., Lindegaard, J. C., Davidson, S. E., Varia, M., West, C., Hunter, R., Overgaard, J., and Raleigh, J. A. Invasive oxygen measurements and pimonidazole labeling in human cervix carcinoma. *Int J Radiat Oncol Biol Phys*, *49*: 581-586, 2001.
9. Olive, P. L., Aquino-Parsons, C., MacPhail, S. H., Liao, S. Y., Raleigh, J. A., Lerman, M. I., and Stanbridge, E. J. Carbonic anhydrase 9 as an endogenous marker for hypoxic cells in cervical cancer. *Cancer Res*, *61*: 8924-8929, 2001.
10. Airley, R. E., Loncaster, J., Raleigh, J. A., Harris, A. L., Davidson, S. E., Hunter, R. D., West, C. M., and Stratford, I. J. GLUT-1 and CAIX as intrinsic markers of hypoxia in carcinoma of the cervix: Relationship to pimonidazole binding. *Int. J. Cancer*, *104*: 85-91, 2003.
11. Azuma, Y., Chou, S. C., Lininger, R. A., Murphy, B. J., Varia, M. A., and Raleigh, J. A. Hypoxia and differentiation in squamous cell carcinomas of the uterine cervix: pimonidazole and involucrin. *Clin Cancer Res*, *9*: 4944-4452, 2003.
12. Nordmark, M., Loncaster, J., Aquino-Parsons, C., Chou, S. C., Ladekarl, M., Havsteen, H., Lindegaard, J. C., Davidson, S. E., Varia, M., West, C., Hunter, R., Overgaard, J., and Raleigh, J. A. Measurements of hypoxia using pimonidazole and polarographic oxygen-sensitive electrodes in human cervix carcinomas. *Radiother Oncol*, *67*: 35-44, 2003.
13. Murdoch, C., Giannoudis, A., and Lewis, C. E. Mechanisms regulating the recruitment of macrophages into hypoxic areas of tumors and other ischemic tissues. *Blood*, *104*: 2224-2234, 2004.
14. Nordmark, M., Loncaster, J., Aquino-Parsons, C., Chou, S.-C., Gebiski, V., West, C., Lindegaard, J. C., Havsteen, H., Davidson, S.E., Hunter, R., Raleigh, J.A. and Overgaard, J. The prognostic value of pimonidazole and tumour pO(2) in human

cervix carcinomas after radiation therapy: A prospective international multi-center study, *Radiother Oncol*, 2006 (on line in advance of print).

### ***Colorectal***

1. Goethals, L., Debucquoy, A., Perneel, C., Geboes, K., Ectors, N., De Schutter, H., Penninckx, F., McBride, W. H., Begg, A. C., and Haustermans, K. M. Hypoxia in human colorectal adenocarcinoma: Comparison between extrinsic and potential intrinsic hypoxia markers. *Int J Radiat Oncol Biol Phys*, 65: 246-254, 2006.
2. van Laarhoven, H. W., Kaanders, J. H., Lok, J., Peeters, W. J., Rijken, P. F., Wiering, B., Ruers, T. J., Punt, C. J., Heerschap, A., and van der Kogel, A. J. Hypoxia in relation to vasculature and proliferation in liver metastases in patients with colorectal cancer. *Int J Radiat Oncol Biol Phys*, 64: 473-482, 2006.

### ***Head and Neck***

1. Raleigh, J. A., Calkins-Adams, D. P., Rinker, L. H., Ballenger, C. A., Weissler, M. C., Fowler, W. C., Jr., Novotny, D. B., and Varia, M. A. Hypoxia and vascular endothelial growth factor expression in human squamous cell carcinomas using pimonidazole as a hypoxia marker. *Cancer Res*, 58: 3765-3768, 1998.
2. Haustermans, K., Hofland, I., Van de Pavert, L., Geboes, K., Varia, M., Raleigh, J., and Begg, A. C. Diffusion limited hypoxia estimated by vascular image analysis: comparison with pimonidazole staining in human tumors. *Radiother Oncol*, 55: 325-333, 2000.
3. Raleigh, J. A., Chou, S. C., Calkins-Adams, D. P., Ballenger, C. A., Novotny, D. B., and Varia, M. A. A clinical study of hypoxia and metallothionein protein expression in squamous cell carcinomas. *Clin Cancer Res*, 6: 855-862, 2000.
4. Wijffels, K. I., Kaanders, J. H., Rijken, P. F., Bussink, J., van den Hoogen, F. J., Marres, H. A., de Wilde, P. C., Raleigh, J. A., and van der Kogel, A. J. Vascular architecture and hypoxic profiles in human head and neck squamous cell carcinomas. *Br J Cancer*, 83: 674-683, 2000.
5. Raleigh, J. A., Chou, S. C., Bono, E. L., Thrall, D. E., and Varia, M. A. Semiquantitative immunohistochemical analysis for hypoxia in human tumors. *Int J Radiat Oncol Biol Phys*, 49: 569-574, 2001.
6. Raleigh, J. A., Thrall, D. E., and Varia, M. A. Development and clinical application of pimonidazole as a marker for tumor hypoxia. *Recent Res. Devel. Cancer*, 3: 189-201, 2001.
7. Begg, A. C., Janssen, H., Sprong, D., Hofland, I., Blommestijn, G., Raleigh, J. A., Varia, M., Balm, A., Van Velthuyzen, L., Delaere, P., Sciort, R., and Haustermans, K. M. G. Hypoxia and perfusion measurements in human tumors--initial experience with pimonidazole and IUdR. *Acta Oncol*, 40: 924-928, 2001.
8. Hoebbers, F. J., Janssen, H. L., Olmos, A. V., Sprong, D., Nunn, A. D., Balm, A. J., Hoefnagel, C. A., Begg, A. C., Haustermans, K. M., Ljungkvist, A. S., Bussink, J., Rijken, P. F., Kaanders, J. H., van der Kogel, A. J., Denekamp, J., and Bonn, D. Phase 1 study to identify tumour hypoxia in patients with head and neck cancer using technetium-99m BRU 59-21. Vascular architecture, hypoxia, and

- proliferation in first-generation xenografts of human head-and-neck squamous cell carcinomas. Why do hypoxic cells behave badly? *Eur J Nucl Med Mol Imaging*, 29: 1206-1211, 2002.
9. Janssen, H. L., Haustermans, K. M., Sprong, D., Blommestijn, G., Hofland, I., Hoebers, F. J., Blijweert, E., Raleigh, J. A., Semenza, G. L., Varia, M. A., Balm, A. J., van Velthuysen, M. L., Delaere, P., Sciort, R., and Begg, A. C. HIF-1alpha, pimonidazole, and iododeoxyuridine to estimate hypoxia and perfusion in human head-and-neck tumors. *Int J Radiat Oncol Biol Phys*, 54: 1537-1549, 2002.
  10. Kaanders, J. H., Wijffels, K. I., Marres, H. A., Ljungkvist, A. S., Pop, L. A., van den Hoogen, F. J., de Wilde, P. C., Bussink, J., Raleigh, J. A., and van der Kogel, A. J. Pimonidazole binding and tumor vascularity predict for treatment outcome in head and neck cancer. *Cancer Res.*, 62: 7066-7074, 2002.
  11. Bussink, J., Kaanders, J. H., and van der Kogel, A. J. Tumor hypoxia at the micro-regional level: clinical relevance and predictive value of exogenous and endogenous hypoxic cell markers. *Radiother Oncol*, 67: 3-15, 2003.
  12. Begg, A. C. Is HIF-1alpha a good marker for tumor hypoxia? *Int. J. Radiat. Oncol. Biol. Phys.*, 56: 917-919, 2003.
  13. Chou, S. C., Azuma, Y., Varia, M. A., and Raleigh, J. A. Evidence that involucrin, a marker for differentiation, is oxygen regulated in human squamous cell carcinomas. *Br. J. Cancer*, 90: 728-735, 2004.
  14. Janssen, H. L., Hoebers, F. J., Sprong, D., Goethals, L., Williams, K. J., Stratford, I. J., Haustermans, K. M., Balm, A. J., and Begg, A. C. Differentiation-associated staining with anti-pimonidazole antibodies in head and neck tumors. *Radiother. Oncol.*, 70: 91-97, 2004.
  15. Arcasoy, M. O., Amin, K., Chou, S. C., Haroon, Z. A., Varia, M., and Raleigh, J. A. Erythropoietin and erythropoietin receptor expression in head and neck cancer: relationship to tumor hypoxia. *Clin Cancer Res*, 11: 20-27, 2005.
  16. Janssen, H. L., Haustermans, K. M., Balm, A. J., and Begg, A. C. Hypoxia in head and neck cancer: how much, how important? *Head Neck*, 27: 622-638, 2005.
  17. Hoogsteen, I. J., Peeters, W. J., Marres, H. A., Rijken, P. F., van den Hoogen, F. J., van der Kogel, A. J., and Kaanders, J. H. Erythropoietin receptor is not a surrogate marker for tumor hypoxia and does not correlate with survival in head and neck squamous cell carcinomas. *Radiother Oncol*, 76: 213-218, 2005.

### ***Kidney***

1. Wykoff, C. C., Beasley, N. J., Watson, P. H., Turner, K. J., Pastorek, J., Sibtain, A., Wilson, G. D., Turley, H., Talks, K. L., Maxwell, P. H., Pugh, C. W., Ratcliffe, P. J., and Harris, A. L. Hypoxia-inducible expression of tumor-associated carbonic anhydrases. *Cancer Res*, 60: 7075-7083, 2000.

### ***Prostate***

1. Carnell, D. M., Smith, R. E., Daley, F. M., Saunders, M. I., Bentzen, S. M., and Hoskin, P. J. An immunohistochemical assessment of hypoxia in prostate

carcinoma using pimonidazole: Implications for radioresistance. *Int J Radiat Oncol Biol Phys*, 65: 91-99, 2006.