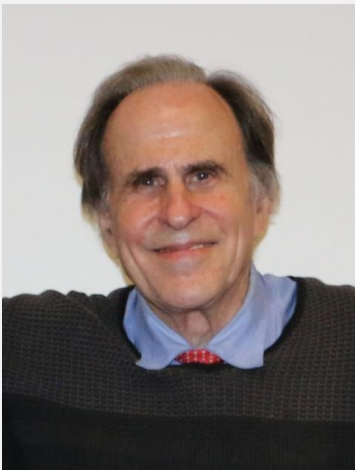


The Multiple Uses of Fluorescent Proteins to Visualize Cancer *In Vivo*



Prof. Robert M. Hoffman

AntiCancer Inc.; Department of Surgery, University of California, San Diego

Naturally fluorescent proteins have revolutionized biology by enabling what was formerly invisible to be seen clearly. These proteins have allowed us to visualize, in real time, important aspects of cancer in living animals, including tumor cell mobility, invasion, metastasis and angiogenesis. These multi-colored proteins have allowed the color-coding of cancer cells growing *in vivo* and enabled the distinction of host from tumor with single-cell resolution. Visualization of many aspects of cancer initiation and progression *in vivo* are possible with fluorescent proteins.

ROBERT M. HOFFMAN

CURRICULUM VITAE

51 YEARS OF SCIENCE

OFFICES:

AntiCancer, Inc.
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San Diego, California 92111
TEL: (858) 654-2555
FAX: (858) 268-4175

Department of Surgery
University of California, San Diego
Medical Center
200 West Arbor Drive
San Diego, California 92103-8402
TEL: (619) 543-6890
FAX: (619) 543-3763

BIRTH DATE:

June 19, 1944

Greenwich, Connecticut

EDUCATION:

Ph.D. (Biology) 1971

Harvard University

Cambridge, Massachusetts

B.A. (Biology) 1965

State University of New York

Buffalo, New York

PRESENT POSITIONS:

President, Chairman of Board and CEO
1984-present

AntiCancer, Inc.

San Diego, California

Professor 1995-present

Department of Surgery
University of California, San Diego
Medical Center
200 West Arbor Drive
San Diego, California 92103-8220

CEO

Robert M. Hoffman Foundation for Cancer
Research 2012-present

MAJOR RESEARCH ACCOMPLISHMENTS:

1) I was the first to discover a mutant in energy metabolism:

- Hoffman, R.M., and Raper, J.R. Genetic restriction of energy conservation in *Schizosaccharomyces pombe*. *Science* **171**, 418-419, 1971

2) I was the first to demonstrate altered DNA methylation in human cancer:

- Diala, E.S. and Hoffman, R.M. Hypomethylation of HeLa cell DNA and the absence of 5-methylcytosine in SV40 and adenovirus (type 2) DNA: analysis by HPLC. *Biochem. Biophys. Res. Commun.* **107**, 19-26, 1982.
- Diala, E.S., Cheah, M.S.C., Rowitch, D. and Hoffman, R.M. Extent of DNA methylation in human tumor cells. *J. Natl. Cancer Inst.* **71**, 755-764, 1983.

3) I was the first to demonstrate altered DNA methylation in an oncogene:

- Cheah, M.S., Wallace, C.D. and Hoffman, R.M. Hypomethylation of DNA in human cancer cells: a site-specific change in the c-myc oncogene. *J. Natl. Cancer Inst.* **73**, 1057-1065, 1984.

4) I was the first to demonstrate altered general methionine metabolism in cancer, the only known general metabolic defect:

- Hoffman, R.M. and Erbe, R.W. High *in vivo* rates of methionine biosynthesis in transformed human and malignant rat cells auxotrophic for methionine. *Proc. Natl. Acad. Sci. USA* **73**, 1523-1527, 1976.
- Hoffman, R.M., Jacobsen, S.J. and Erbe, R.W. Reversion to methionine independence in simian virus 40-transformed human and malignant rat fibroblasts is associated with altered ploidy and altered properties of transformation. *Proc. Natl. Acad. Sci. USA* **76**, 1313-1317, 1979.
- Coalson, D.W., Mecham, J.O., Stern, P.H., and Hoffman, R.M. Reduced availability of endogenously synthesized methionine for S-adenosylmethionine formation in methionine-dependent cancer cells. *Proc. Natl. Acad. Sci. USA* **79**, 4248-4251, 1982.

- Stern, P.H., Mecham, J.O., Wallace, C.D. and Hoffman, R.M. Reduced free-methionine in methionine-dependent SV40-transformed human fibroblasts synthesizing apparently normal amounts of methionine. *J. Cell. Physiol.* **117**, 9-14, 1983.
- Stern, P.H., and Hoffman, R.M. Elevated overall rates of transmethylation in cell lines from diverse human tumors. *In Vitro* **20**, 663-670, 1984.

5) I pioneered the field of cancer epigenetics:

- Hoffman, R.M. Altered methionine metabolism, DNA methylation and oncogene expression in carcinogenesis. A review and synthesis. *Biochim. Biophys. Acta* **738**, 49-87, 1984.

6) I pioneered the field of methionine-deprivation cancer therapy:

- Stern, P.H. and Hoffman, R.M. Enhanced in vitro selective toxicity of chemotherapeutic agents for human cancer cells based on a metabolic defect. *J. Natl. Cancer Inst.* **76**, 629-639, 1986
- Sun, X., Yang, Z., Li, S., Tan, Y., Zhang, N., Wang, X., Yagi, S., Yoshioka, T., Takimoto, A., Mitsushima, K., Suginaka, A., Frenkel, E.P., and Hoffman, R.M. *In vivo* efficacy of recombinant methioninase is enhanced by the combination of polyethylene glycol conjugation and pyridoxal 5' phosphate supplementation. *Cancer Research* **63**, 8377-8383, 2003.
- Yang, Z., Wang, J., Yoshioka, T., Li, B., Lu, Q., Li, S., Sun, X., Tan, Y., Yagi, S., Frenkel, E.P., and Hoffman, R.M. Pharmacokinetics, methionine depletion, and antigenicity of recombinant methioninase in primates. *Clinical Cancer Research* **10**, 2131-2138, 2004.
- Yang, Z., Sun, X., Li, S., Tan, Y., Wang, X., Zhang, N., Yagi, S., Takakura, T., Kobayashi, Y., Takimoto, A., Yoshioka, T., Suginaka, A., Frenkel, E.P., and Hoffman, R.M. Circulating half-life of PEGylated recombinant methioninase holoenzyme is highly dose dependent on cofactor pyridoxal-5'-phosphate. *Cancer Research* **64**, 5775-5778, 2004.
- Yang, Z., Wang, J., Lu, Q., Xu, J., Kobayashi, Y., Takakura, T., Takimoto, A., Yoshioka, T., Lian, C., Chen, C., Zhang, D., Zhang, Y., Li, S., Sun, X., Tan, Y., Yagi, S., Frenkel, E.P., and Hoffman, R.M. PEGylation confers greatly extended half-life and attenuated immunogenicity to recombinant methioninase in primates. *Cancer Research* **64**, 6673-6678, 2004.

7) I was the first to compare gene expression in normal and cancer cells:

- Williams, J., Hoffman, R.M. and Penman, S. The extensive homology between mRNA sequences of normal and SV40-transformed human fibroblasts. *Cell* **11**, 901-907, 1977.

8) I pioneered the field of non-viral gene therapy:

- Hoffman, R.M., Margolis, L.B. and Bergelson, L.D. Binding and entrapment of high molecular weight DNA by lecithin liposomes. *FEBS Letters* **93**, 365-368, 1978.

- Li, L., Hoffman, R.M. The feasibility of targeted selective gene therapy of the hair follicle. *Nature Medicine* 1, 705-706, 1995.

9) I developed the first practical *in vitro* drug response assay for human cancer patients to enable individualized cancer therapy: :\\wpdocs\CV\RMH-CV cutoff 6-9 Page 6

- Freeman, A.E. and Hoffman, R.M. In vivo-like growth of human tumors in vitro. *Proc. Natl. Acad. Sci. USA* 83, 2694-2698, 1986.
- Vescio, R.A., Redfern, C.H., Nelson, T.J., Ugoretz, S. Stern, P.H. and Hoffman, R.M. *In vivo*-like drug responses of human tumors growing in three-dimensional gel-supported, primary culture. *Proc. Natl. Acad. Sci. USA* 84, 5029-5033, 1987.
- Furukawa, T., Kubota, T., Hoffman, R.M. Clinical applications of the histoculture drug response assay. *Clinical Cancer Research* 1, 305-311, 1995.
- Kubota, T., Sasano, N., Abe, O., Nakao, I., Kawamura, E., Saito, T., Endo, M., Kimura, K., Demura, H., Sasano, H., Nagura, H., Ogawa, N., Hoffman, R.M. Potential of the histoculture drug response assay to contribute to cancer patient survival. *Clinical Cancer Research* 1, 1537-1543, 1995.

10) I pioneered the field of culturing hair-growing skin:

- Li, L., Margolis, L.B. and Hoffman, R.M. Skin toxicity determined *in vitro* by three-dimensional, native-state histoculture. *Proc. Natl. Acad. Sci. USA* 88, 1908-1912, 1991.
- Li, L., Margolis, L.B., Paus, R. and Hoffman, R.M. Hair shaft elongation, follicle growth, and spontaneous regression in long-term, gelatin sponge-supported histoculture of human scalp skin. *Proc. Natl. Acad. Sci. USA* 89, 8764-8768, 1992.

11) I developed the first clinically-relevant mouse models of human cancer:

- Fu, X.Y., Besterman, J.M., Monosov, A. and Hoffman, R.M. Models of human metastatic colon cancer in nude mice orthotopically constructed by using histologically intact patient specimens. *Proc. Natl. Acad. Sci. USA* 88, 9345-9349, 1991.
- Fu, X., Guadagni, F. and Hoffman, R.M. A metastatic nude-mouse model of human pancreatic cancer constructed orthotopically from histologically intact patient specimens. *Proc. Natl. Acad. Sci. USA* 89, 5645-5649, 1992.

12) I discovered the specific role of the host organ in cancer growth:

- Togo, S., Shimada, H., Kubota, T., Moossa, A.R., Hoffman, R.M. Host organ specifically determines cancer progression. *Cancer Res.* 55, 681-684, 1995.

13) I discovered the governing step of metastasis:

- Kuo, T-H., Kubota, T., Watanabe, M., Furukawa, T., Teramoto, T., Ishibiki, K., Kitajima, M., Moossa, A.R., Penman, S., Hoffman, R.M. Liver colonization competence governs colon cancer metastasis. *Proc. Natl. Acad. Sci. USA* 92, 12085-12089, 1995.

14) I co-discovered the genetic basis of cell senescence:

- Schmitt, C.A., Fridman, J.S., Yang, M., Baranov, E., Hoffman, R.M. and Lowe, S.W. Dissecting p53 tumor suppressor functions *in vivo*. *Cancer Cell* **1**, 289-298, 2002 (Cover story).
- Schmitt, C.A., Fridman, J.S., Yang, M., Lee, S., Baranov, E., Hoffman, R.M., and Lowe, S.W. A senescence program controlled by p53 and p16INK4a contributes to the outcome of cancer therapy. *Cell* **109**, 335-346, 2002.

15) I pioneered *in vivo* imaging using fluorescent proteins:

- Hoffman, R.M. The multiple uses of fluorescent proteins to visualize cancer *in vivo*. *Nature Reviews Cancer* **5**, 796-806, 2005.
- Chishima, T., Miyagi, Y., Wang, X., Yamaoka, H., Shimada, H., Moossa, A.R. and Hoffman, R.M. Cancer invasion and micrometastasis visualized in live tissue by green fluorescent protein expression. *Cancer Research* **57**, 2042-2047, 1997.
- Naumov, G.N., Wilson, S.M., MacDonald, I.C., Schmidt, E.E., Morris, V.L., Groom, A.C., Hoffman, R.M., Chambers, A.F. Cellular expression of green fluorescent protein, coupled with high-resolution *in vivo* videomicroscopy, to monitor steps in tumor metastasis. *J. Cell Sci.* **112**, 1835-1842, 1999.
- Yang, M., Baranov, E., Jiang, P., Sun, F-X., Li, X-M., Li, L., Hasegawa, S., Bouvet, M., Al-Tuwaijri, M., Chishima, T., Shimada, H., Moossa, A.R., Penman, S., Hoffman, R.M. Whole-body optical imaging of green fluorescent protein-expressing tumors and metastases. *Proc. Natl. Acad. Sci. USA* **97**, 1206-1211, 2000.
- Yang, M., Baranov, E., Moossa, A.R., Penman, S., Hoffman, R.M. Visualizing gene expression by whole-body fluorescence imaging. *Proc. Natl. Acad. Sci. USA* **97**, 12278-12282, 2000.
- Yang, M., Baranov, E., Li, X-M., Wang, J-W., Jiang, P., Li, L., Moossa, A.R., Penman, S., Hoffman, R.M. Whole-body and intravital optical imaging of angiogenesis in orthotopically implanted tumors. *Proc. Natl. Acad. Sci. USA* **98**, 2616-2621, 2001.
- Zhao, M., Yang, M., Baranov, E., Wang, X., Penman, S., Moossa, A.R., and Hoffman, R.M. Spatial-temporal imaging of bacterial infection and antibiotic response in intact animals. *Proc. Natl. Acad. Sci. USA* **98**, 9814-9818, 2001.
- Yang, M., Baranov, E., Wang, J-W., Jiang, P., Wang, X., Sun, F-X., Bouvet, M., Moossa, A.R., Penman, S., and Hoffman, R.M. Direct external imaging of nascent cancer, tumor progression, angiogenesis, and metastasis on internal organs in the fluorescent orthotopic model. *Proc. Natl. Acad. Sci. USA* **99**, 3824-3829, 2002.
- Bouvet, M., Wang, J-W., Nardin, S.R., Nassirpour, R., Yang, M., Baranov, E., Jiang, P., Moossa, A.R., and Hoffman, R.M. Real-time optical imaging of primary tumor growth and multiple metastatic events in a pancreatic cancer orthotopic model. *Cancer Research* **62**, 1534-1540, 2002 (Cover story).
- Yang, M., Li, L., Jiang, P., Moossa, A.R., Penman, S., and Hoffman, R.M. Dual-color fluorescence imaging distinguishes tumor cells from induced host angiogenic vessels and stromal cells. *Proc. Natl. Acad. Sci. USA* **100**, 14259-14262, 2003.

- Mitsiades, C.S., Mitsiades, N.S., Bronson, R.T., Chauhan, D., Munshi, N., Treon, S.P., Maxwell, C.A., Pilarski, L., Hideshima, T., Hoffman, R.M., and Anderson, K.C. Fluorescence imaging of multiple myeloma cells in a clinically relevant SCID/NOD *in vivo* model: biologic and clinical implications. *Cancer Research* **63**, 6689-6696, 2003.
- Yamamoto, N., Jiang, P., Yang, M., Xu, M., Yamauchi, K., Tsuchiya, H., Tomita, K., Wahl, G.M., Moossa, A.R., and Hoffman, R.M. Cellular dynamics visualized in live cells *in vitro* and *in vivo* by differential dual-color nuclear-cytoplasmic fluorescent-protein expression. *Cancer Research* **64**, 4251-4256, 2004.
- Simberg, D., Duza, T., Park, J.H., Essler, M., Pilch, J., Zhang, L., Derfus, A.M., Yang, M., Hoffman, R.M., Bhatia, S., Sailor, M.J., and Ruoslahti, E. Biomimetic amplification of nanoparticle homing to tumors. *Proc. Natl. Acad. Sci. USA* **104**, 932-936, 2007.
- Hoffman, R.M., and Yang, M. Color-coded fluorescence imaging of tumor-host interactions. *Nature Protocols* **1**, 928-935, 2006.
- Hoffman, R.M., and Yang, M. Subcellular imaging in the live mouse. *Nature Protocols* **1**, 775-782, 2006.
- Hoffman, R.M., and Yang, M. Whole-body imaging with fluorescent proteins. *Nature Protocols* **1**, 1429-1438, 2006.

16) I was the first to image the tumor microenvironment:

- Yang, M., Jiang, P., and Hoffman, R.M. Whole-body subcellular multicolor imaging of tumor-host interaction and drug response in real time. *Cancer Research* **67**, 5195-5200, 2007.

17) I discovered the only known adult pluripotent stem cells:

- Li, L., Mignone, J., Yang, M., Matic, M., Penman, S., Enikolopov, G., and Hoffman, R.M. Nestin expression in hair follicle sheath progenitor cells. *Proc. Natl. Acad. Sci. USA* **100**, 9958-9961, 2003.
- Amoh, Y., Li, L., Yang, M., Moossa, A.R., Katsuoka, K., Penman, S., and Hoffman, R.M. Nascent blood vessels in the skin arise from nestin-expressing hair follicle cells. *Proc. Natl. Acad. Sci. USA* **101**, 13291-13295, 2004.
- Amoh, Y., Li, L., Campillo, R., Kawahara, K., Katsuoka, K., Penman, S., and Hoffman, R.M. Implanted hair follicle stem cells form Schwann cells that support repair of severed peripheral nerves. *Proc. Natl. Acad. Sci. USA* **102**, 17734-17738, 2005.
- Amoh, Y., Li, L., Katsuoka, K., Penman, S., and Hoffman, R.M. Multipotent nestin-positive, keratin-negative hair-follicle bulge stem cells can form neurons. *Proc. Natl. Acad. Sci. USA* **102**, 5530-5534, 2005.

18) I was the first to determine what controlled the clonality of metastasis:

- Yamamoto, N., Yang, M., Jiang, P., Xu, M., Tsuchiya, H., Tomita, K., Moossa, A.R., and Hoffman, R.M. Determination of clonality of metastasis by cell-specific color-coded fluorescent-protein imaging. *Cancer Research* **63**, 7785-7790, 2003.

19) I discovered the first bacteria that specifically target and can completely eradicate cancer:

- Zhao, M., Yang, M., Li, X-M., Jiang, P., Baranov, E., Li, S., Xu, M., and Hoffman, R.M. Tumor-targeting bacterial therapy with amino acid auxotrophs of GFP-expressing *Salmonella typhimurium*. Proc. Natl. Acad. Sci. USA **102**, 755-760, 2005.
- Zhao, M., Yang, M., Ma, H., Li, X., Tan, X., Li, S., Yang, Z., and Hoffman, R.M. Targeted therapy with a *Salmonella typhimurium* leucine-arginine auxotroph cures orthotopic human breast tumors in nude mice. Cancer Research **66**, 7647-7652, 2006.
- Zhao, M., Geller, J., Ma, H., Yang, M., Penman, S., and Hoffman, R.M. Monotherapy with a tumor-targeting mutant of *S. typhimurium* cures orthotopic metastatic mouse models of human prostate cancer. Proc. Natl. Acad. Sci. USA **104**, 10170-10174, 2007.
- Arrach, N., Zhao, M., Porwollik, S., Hoffman, R.M., and McClelland, M. *Salmonella* promoters preferentially activated inside tumors. Cancer Research **68**, 4827-4832, 2008.

20) I discovered that passenger stromal cells are necessary for metastasis:

- Bouvet, M., Tsuji, K., Yang, M., Jiang, P., Moossa, A.R., and Hoffman, R.M. *In vivo* color-coded imaging of the interaction of colon cancer cells and splenocytes in the formation of liver metastases. Cancer Research **66**, 11293-11297, 2006.

21) I discovered the mechanism of chemotherapy-induced alopecia:

- Amoh, Y., Li, L., Moossa, A.R., Katsuoka, K., and Hoffman, R.M. Chemotherapy targets the hair-follicle vascular network but not the stem cells. J. Invest. Dermatol. **127**, 11-15, 2007.

22) I developed the first recombinant enzyme-based diagnostics for homocysteine, vitamin B6 and cysteine:

- Tan, Y., and Hoffman, R.M. A highly sensitive single-enzyme homocysteine assay. Nature Protocols **3**, 1388-1394, 2008.
- Han, Q., and Hoffman, R.M. Enzymatic assay for total plasma Cys. Nature Protocols **3**, 1778-1781, 2008.
- Han, Q., and Hoffman, R.M. **3**, 1815-1819, 2008. Nonradioactive enzymatic assay for plasma and serum vitamin B6. Nature Protocols.

23) I developed the basis for fluorescence-guided cancer surgery:

- Kishimoto, H., Zhao, M., Hayashi, K., Urata, Y., Tanaka, N., Fujiwara, T., Penman, S., and Hoffman, R.M. *In vivo* internal tumor illumination by telomerase-dependent adenoviral GFP for precise surgical navigation. Proc. Natl. Acad. Sci. USA **106(34)**, 14514-14517, 2009.
- Green Surgery, Barbara R. Jasny, Editors' Choice. Science **325**, 1321, 11 September 2009.

24) I co-discovered that blood vessels in tumors can be formed from cancer cells:

- Soda, Y., Marumoto, T., Friedmann-Morvinski, D., Soda, M., Liu, F., Michiue, H., Pastorino, S., Yang, M., Hoffman, R.M., Kesari, S., Verma, I.M. Transdifferentiation of glioblastoma cells into vascular endothelial cells. *Proc. Natl. Acad. Sci. USA* **108**, 4274-4280, 2011 (Cover story).

25) I co-discovered that tumor-infiltrating T-cells stimulate cancer metastasis:

- Tan, W., Zhang, W., Strasner, A., Grivennikov, S., Cheng, J.Q., Hoffman, R.M., and Karin, M. Tumour-infiltrating regulatory T cells stimulate mammary cancer metastasis through RANKL-RANK signaling. *Nature* **470**, 548-553, 2011.

POSTDOCTORAL TRAINING:

1971-1973

Department of Biology

Harvard University

With the late Professor John R. Raper

1973-1975

Massachusetts General Hospital Harvard Medical School

With Dr. Richard W. Erbe and Professor John W. Littlefield

1976-1977

USA-USSR National Academy of Sciences Exchange Fellow

The Shemyakin Institute of Bioorganic Chemistry

Academy of Sciences, Moscow, USSR

With Professor L.D. Bergelson

1976-1977

Weizmann Institute of Science 1978

Rehovot, Israel

With Dr. Carol Prives

PREVIOUS ACADEMIC POSITIONS:

1975-1979

Instructor of Pediatrics Harvard Medical School

Massachusetts General Hospital

1979-1983

Assistant Professor, Department of Pediatrics University of California, San Diego
School of Medicine

1983-1990

Associate Professor, Department of Pediatrics University of California, San Diego
School of Medicine

1990-1995

Professor, Department of Pediatrics University of California, San Diego
School of Medicine

PROFESSIONAL SOCIETIES:

1. Society for *In Vitro* Biology
2. American Association of Cancer Research
3. American Society for Clinical Oncology
4. Society of Surgical Oncology
5. American Society for Cell Biology
6. Metastasis Research Society
7. Japanese Cancer Association
8. Japanese Society of Clinical Oncology (First American Member)
9. Japanese Metastasis Research Society (First American Member)
10. Japanese Society of Human Cell
11. Preclinical Therapeutic Model Group of the European Organization for Research and Treatment of Cancer
12. Chinese Society for Clinical Oncology (First American Member)
13. International Society for Stem Cell Research

BOARDS:

1986-present

Ad-Hoc Reviewer

National Cancer Institute

EDITORIAL BOARDS:

Anticancer Research 1985-present

In Vitro Cellular and Developmental Biology 1987-present

Associate Editor, *Clinical Cancer Research* 2000-Present

Academic Editor, *PLOS ONE* 2015-Present

Editorial Advisory Board, *Journal of Fluorescence Guided Surgery* 2015-Present

TEACHING AT THE UNIVERSITY OF CALIFORNIA, SAN DIEGO:

Biology 112:

"Cell and Molecular Biology"

Spring and Fall 1980, with Professor Gordon Sato

Pediatrics 233:

"Genes and Cancer"

Winter 1982-1994

Pediatrics 235: "New Biological Approaches to Cancer Prevention and Treatment"

Spring 1983-1994

Pediatrics 237: "Biochemical Genetics of Aging"

Fall 1984-1994

SCIENTIFIC MENTORING OF SURGICAL RESIDENTS AT UCSD

Reza Gamagami, M.D. (1994-1996)

Aaron R. Sasson, M.D. (1995-1997)

Babak Rashidi, M.D. (1998-2000)

Maria Al-Tuwaijri, M.D. (2000-2001)

Waddah B. Al-Refaie, M.D. (2000-2001)

Matthew H. G. Katz, M.D. (2002-2004)

Michele McElroy, M.D. (2004-2006)

Hop S. Tran Cao, M.D. (2007-2009)

Cristina Metildi, M.D. (2010-Present)

Ali Maawy, M.D. (2012-Present)

Jonathan Delong, M.D. (2015-Present)

Most Cited Publications of Robert M. Hoffman (1-100)

Total unique citations: 32,194 (ISI: 20,592) (Google: 29,540) (Scopus: 18,327)

h-index = 94 (94 publications with at least 94 citations each)

1. Schmitt, C.A., Fridman, J.S., Yang, M., Lee, S., Baranov, E., Hoffman, R.M., and Lowe, S.W. A senescence program controlled by p53 and p16INK4a contributes to the outcome of cancer therapy. *Cell* 109, 335-346, 2002. (Total unique citations: 834) (ISI: 539) (Google: 782) (Scopus: 574)
2. Yang, M., Baranov, E., Jiang, P., Sun, F-X., Li, X-M., Li, L., Hasegawa, S., Bouvet, M., Al-Tuwaijri, M., Chishima, T., Shimada, H., Moossa, A.R., Penman, S., Hoffman, R.M. Whole-body optical imaging of green fluorescent protein-expressing tumors and metastases. *Proc. Natl. Acad. Sci. USA* 97, 1206-1211, 2000. (Total unique citations: 609) (ISI: 361) (Google: 575) (Scopus: 368)
3. Hoffman, R.M. The multiple uses of fluorescent proteins to visualize cancer in vivo. *Nature Reviews Cancer* 5, 796- 806, 2005. (Total unique citations: 527) (ISI: 393) (Google: 511) (Scopus: 391)
4. Hoffman, R.M. Orthotopic metastatic mouse models for anticancer drug discovery and evaluation: a bridge to the clinic. *Investigational New Drugs* 17, 343-359, 1999. (Total unique citations: 490) (ISI: 308) (Google: 474) (Scopus: 334)
5. Schmitt, C.A., Fridman, J.S., Yang, M., Baranov, E., Hoffman, R.M. and Lowe, S.W. Dissecting p53 tumor suppressor functions in vivo. *Cancer Cell* 1, 289-298, 2002 (Cover story). (Total unique citations: 481) (ISI: 338) (Google: 468) (Scopus: 351)
6. Hoffman, R.M. Altered methionine metabolism, DNA methylation and oncogene expression in carcinogenesis. A review and synthesis. *Biochim. Biophys. Acta* 738, 49-87, 1984. (Total unique citations: 411) (ISI: 307) (Google: 355) (Scopus: 38)
7. Glinsky, G.V., Glinskii, A.B., Stephenson, A.J., Hoffman, R.M., and Gerald, W.L. Gene expression profiling predicts clinical outcome of prostate cancer. *J. Clin. Investig.* 113, 913-923, 2004. (Total unique citations: 402) (ISI: 250) (Google: 378) (Scopus: 258)
8. Amoh, Y., Li, L., Katsuoka, K., Penman, S., and Hoffman, R.M. Multipotent nestin-positive, keratin-negative hair-follicle bulge stem cells can form neurons. *Proc. Natl. Acad. Sci. USA* 102, 5530-5534, 2005. (Total unique citations: 389) (ISI: 229) (Google: 372) (Scopus: 240)
9. Kioi, M., Vogel, H., Schultz, G., Hoffman, R.M., Harsh, G.R., and Brown, J.M. Inhibition of vasculogenesis, but not angiogenesis, prevents the recurrence of glioblastoma following irradiation in mice. *J. Clin. Investig.* 120, 694-705, 2010. (Total unique citations: 367) (ISI: 259) (Google: 351) (Scopus: 283)
10. Chishima, T., Miyagi, Y., Wang, X., Yamaoka, H., Shimada, H., Moossa, A.R. and Hoffman, R.M. Cancer invasion and micrometastasis visualized in live tissue by green fluorescent protein expression. *Cancer Research* 57, 2042-2047, 1997. (Total unique citations: 348) (ISI: 227) (Google: 314) (Scopus: 224)
11. Simberg, D., Duza, T., Park, J.H., Essler, M., Pilch, J., Zhang, L., Derfus, A.M., Yang, M., Hoffman, R.M., Bhatia, S., Sailor, M.J., and Ruoslahti, E. Biomimetic

- amplification of nanoparticle homing to tumors. *Proc. Natl. Acad. Sci. USA* 104, 932-936, 2007. (Total unique citations: 343) (ISI: 200) (Google: 318) (Scopus: 216)
12. Wang, X., Fu, X., Brown, P.D., Crimmin, M.J. and Hoffman, R.M. Matrix metalloproteinase inhibitor BB-94 (batimastat) inhibits human colon tumor growth and spread in a patient-like orthotopic model in nude mice. *Cancer Res.* 54, 4726-4728, 1994. (Total unique citations: 338) (ISI: 239) (Google: 280) (Scopus: 221)
13. Tan, W., Zhang, W., Strasner, A., Grivennikov, S., Cheng, J.Q., Hoffman, R.M., and Karin, M. Tumour-infiltrating regulatory T cells stimulate mammary cancer metastasis through RANKL-RANK signaling. *Nature* 470, 548-553, 2011. (Total unique citations: 294) (ISI: 198) (Google: 281) (Scopus: 137)
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Most Cited Publications of Robert M. Hoffman (101-200)

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