BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Constance E. Brinckerhoff	Professor
eRA COMMONS USER NAME	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Smith College, Northampton, MA	BA cum laude	1963	Biology
SUNY Buffalo	MA	1966	Microbiology/Immunology
SUNY Buffalo	PhD	1968	Microbiology/Immunology

PROFESSIONAL EXPERIENCE

1964 - 1968	Predoctoral Fellow, Dept. of Microbiology, School of Medicine, SUNY at Buffalo, NY
1969 - 1971	Director of Bacteriology, Brattleboro Memorial Hospital, Brattleboro, Vermont
1970 - 1972	Adjunct Assistant Professor of Microbiology, Windham College, Putney, Vermont
1972 - 1975	Research Associate, Dept. of Microbiology, Dartmouth Medical School (DMS), Hanover, NH
1975 - 1976	Instructor in Microbiology, DMS, Hanover, NH
1977 - 1978	Instructor in Medicine, DMS, Hanover, NH
1978 - 1982	Research Assistant Professor of Medicine, DMS, Hanover, NH
1982 - 1984	Research Associate Professor of Medicine, DMS, Hanover, NH
1984 - 1988	Associate Professor of Medicine and Biochemistry, DMS, Hanover, NH
1988 - current	Professor of Medicine and Biochemistry, DMS, Hanover, NH
1989 - 1991	Acting Chair, Biochemistry, DMS, Hanover, NH
1991 - current	Associate Dean of Science, DMS, Hanover, NH
1991 - 1993	Oscar Cohn Distinguished Professor of Molecular Medicine, DMS, Hanover, NH
1993 - current	Nathan Smith Professor of Medicine and Biochemistry, DMS, Hanover, NH
1998 - 1999	Acting Provost, Dartmouth College, Hanover, NH

HONORS AND FELLOWSHIPS

1963	Sigma Xi
1963	Smith College Prize for Excellence in Microbiology
1973 - 1975	NIH Postdoctoral Fellow
1974 - 1976	Fellow of the Leukemia Society of America
1981	Travel Fellowship; International Meeting of the League against Rheumatism (Paris, France)
1984 - 1988	Member, Pathobiological Chemistry Study Section NIH
1985 - 1988	Recipient of "Devil's Bag Award", National Arthritis Foundation
1987 - 1992	Member, Arthritis Foundation Research Committee
1990 - 1995	Member, Recombinant DNA Advisory Committee, NIH
1990 - 1995	Editorial Board, Arthritis and Rheumatism
1992	Co-Founder and Chair, Gordon Conference on Matrix Metalloproteinases (Plymouth, NH, 8/93)
1996	Ninth Annual Presidential Lecturer, Dartmouth College, Hanover, NH
1996 - 2000	Member, Pathological Chemistry Study Section, NIH
1996	Member, Blue Ribbon Panel of the Arthritis Foundation to assess research goals
1999 - 2004	Editorial Board, *Journal of Biological Chemistry*
1999 - 2007	MERIT Award, National Institute Arthritis and Musculo-Skeletal Disease. NIH
2003 -	Executive Editor, *J. Cellular Physiology*
2003	Recipient of Smith College Medal for Distinction in Teaching and Research

2004 Distinguished Small Group Leader Award, DMS I
2005 Member, Special Panel to Review of the Organizational Structure of the NIAMS Extramural Program
2006 Member, Special Review Panel on Tumor Microenvironment (NCI)
2007 - Editorial Board, *Journal of Biological Chemistry*
2007 - Member, Arthritis, Connective Tissue and Skin Study Section, NIIH
2008 Honored as a "MASTER" by the American College of Rheumatology
2009 Member, Special Emphasis Review Panel, NCI

PUBLICATIONS (partial listing from more than 140)

1. Vincenti, M.P., Clark, I.M, and Brinckerhoff, C.E., Using inhibitors of metalloproteinases to treat arthritis: easier said than done? Arthr. and Rheum, 37: 1115-1126,1994
2. Vincenti, M.P., Coon, C.I. Lee,O. and Brinckerhoff, C.E., Regulation of collagenase gene expression by IL-1 ß requires transcriptional and post-transcriptional mechanisms. Nucleic Acids Research 22:4818-4827, 1994.
3. White, L.A. and Brinckerhoff, C.E. Two AP-1 elements in the collagenase promoter have differential effects on transcription and bind Jun D, c-Fos and Fra-2. Matrix Biology, 14: 715-725, 1995
4. Vincenti, MP, White LA, Schroen DJ, Benbow U and Brinckerhoff CE (1996). Regulating expression of the gene for matrix metalloproteinase-1 (collagenase). Critical Reviews in Eucaryotic Gene Expression, 6:391-411, 1996
5. Benbow U and Brinckerhoff CE. The AP-1 site and MMP gene regulation: what is all the fuss about? Matrix Biology, 15: 519-526,1997
6. Schroen DJ and Brinckerhoff CE. Nuclear hormone receptors inhibit matrix metalloproteinase (MMP) gene expression through diverse mechanisms.Gene Expression, 6:197-207, 1997
7. Rutter JL, Benbow U, Coon CI and Brinckerhoff CE. Cell-type specific regulation of human interstitial collagenase-1 gene expression by interleukin-1ß in human fibroblasts and BC-8701 breast cancer cells. J. Cell. Biochem. 66:322-336, 1997
8. Aikawa M, Rabkin E, Okada Y, Voglic SJ, Clinton SK, Brinckerhoff CE**,** Sukhova GK, and Libby P. Lipid lowering by diet reduces matrix metalloproteinase activity and increases collagen content of rabbit atheroma: a potential mechanism of lesion stabilization. Circulation, 97:2433 - 2444. 1998
9. Vincenti MP, Coon CI and Brinckerhoff CE. NF-kB activates an element in the distal matrix metalloproteinase-1 promoter in interleukin-1ß stimulated rabbit synovial fibroblasts. Arthritis and Rheum, 41: 1987-1994, 1998
10. Rutter JL, Mitchell TI, Buttice G, Meyers J, Gusella JF, Orzelius LJ and Brinckerhoff CE. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter creates an Ets binding site and augments transcription. Cancer Res. 58: 5321-5325, 1998
11. Brinckerhoff CE. The winter of our discontent. Dartmouth Medicine 23:34-37, 1998
12. Benbow U, Rutter JL, Lowrey CH and Brinckerhoff CE. Transcriptional repression of the human collagenase-1 (MMP-1) gene in MDA231 breast cancer cells by all-trans-retinoic acid in human breast cancer cells requires distal regions of the promoter. Br. J. Cancer, 79: 221-228, 1999
13. Benbow U, Maitra R, Hamilton JW and Brinckerhoff CE. Selective modulation of collagenase-1 gene expression by the chemotherapeutic agent Doxorubicin. Clinical Cancer Res. 5: 203-208, 1999
14. Benbow U, Schoenermark MP, Orndorff KA, Given AL and Brinckerhoff CE. Human breast cancer cells activate procollagenase-1 and invade type I collagen: invasion is inhibited by all-trans retinoic acid. Clin. Exp. Metastasis. 17: 213-238, 1999
15. Schoenermark MP, Mitchell TI, Rutter JL, Peczek PR and Brinckerhoff CE. Retinoid-mediate suppression of tumor invasion and matrix metalloproteinase synthesis. Annals NYAS. 878:466-486, 1999
16. Benbow U, Schoenermark MP, Mitchell TI, Rutter JL, Shimokawa K, Nagase H and Brinckerhoff CE. A novel host/tumor cell interaction activates Matrix Metalloproteinase 1 and mediates invasion through type I collagen. J. Biol. Chem. 274: 25371-25378,1999
17. White LA, Mitchell TI and Brinckerhoff CE. Transforming growth factor ß inhibitory element in the rabbit matrix metalloproteinase-1 (collagenase-1) gene functions as a repressor of constitutive transcription. Biochim. Biophys. Acta 1490: 259-268, 2000

18. Menghol JA, Vincenti MP, Coon CI, Barchowsky A and Brinckerhoff CE. IL-1 induction of collagenase 3 (MMP-13) gene expression requires p38, JNK, and NFkB in chondrocytes. Arthritis and Rheum, 43: 801-811, 2000
19. Benbow U, Orndorff KA, Brinckerhoff CE and Given AL. Confocal assay for invasion: use of propidium iodide fluroescence and laser reflectance to quantify the rate of migration of cells through a matrix. Cytometry 40: 253–259, 2000
20. Brinckerhoff CE, Rutter JL and Benbow U. Interstitial collagenases as markers of tumor progression. Clinical Cancer. Res. 6:4823-4830, 2000
21. Noll WW, Belloni DR, Rutter JL, Storm CA, Schned AR, Titus-Ernstoff L, Ernstoff MS and Brinckerhoff CE. Loss of heterozygosity on chromosome 11q22-23 in melanoma is associated with retention of the insertion polymorphism in the matrix metalloproteinase-1 promoter. Am J. Pathol. 158: 691 – 697, 2001
22. Mix KS, Mengshol JA, Benbow U, Vincenti MP, Sporn MB and Brinckerhoff CE. A synthetic triterpenoid selectively inhibits the induction of matrix metalloproteinases 1 and 13 by inflammatory cytokines. Arthr & Rheum. 44:1096-1104. 2001
23. Vincenti MP and Brinckerhoff CE. 2001. The potential of signal transduction inhibitors for the treatment of arthritis: is it all just JNK? J. Clin. Invest. 108(2): 181-183. 2001
24. Vincenti MP and Brinckerhoff CE 2001. Early response genes induced in chondrocytes stimulated with the inflammatory cytokine, Interleukin-1 ß (IL-1 ß). Arthritis Res.3: 381-388, 2001
25. Mengshol JA, Vincenti MP and Brinckerhoff CE. IL-1 induces collagenase-3 (MMP-13) promoter activity in stably transfected chondrocytic cells: requirement for Runx-2 and activation of p38 MAPK and JNK pathways. Nucleic Acids Research. 29: 4361-4372, 2001
26. Tobin SW, Douville K, Benbow U, Brinckerhoff CE, Memoli VA, and Arrick BA Consequences of Altered TGF-ßExpression and Responsiveness in Breast Cancer: Evidence for Autocrine and Paracrine Effects. Oncogene. 21: 108-118, 2002
27. Mengshol JA, Mix KS and Brinckerhoff CE. Matrix metalloproteinases as therapeutic targets in arthritic disease. Bull's eye or missing the mark? Arthritis and Rheum. 46: 13-20, 2002
28. Tower GB, Coon CI, Benbow U, Vincenti MP and Brinckerhoff CE. Erk1/2 differentially regulates the expression from the 1G/2G single nucleotide polymorphism in the MMP-1 promoter in melanoma cells. Biochim. Biophys. Acta. 1586: 265-274, 2002
29. Brinckerhoff CE and Matrisian LM. Matrix metalloproteinases: a tail of a frog that became a prince. Nature Reviews Mol. Cell Biology. 3: 207-214, 2002
30. Vincenti MP and Brinckerhoff CE. Transcriptional regulation of collagense (MMP-1, MMP-13) gene in arthritis: integrationof complex signaling pathways for the recruitment of gene-specific transcription factors. Arthrits. Res. 4: 157-164, 2002
31. Benbow U, Tower GB, Wyatt CA, Buttice G and Brinckerhoff CE. High level of MMP-1 expression in the absence of the 2G nucleotide polymorphism is mediated by p38 and ERK1/2 Mitogen-Activated Protein Kinases in VMM5 melanoma cells. J. Cellular Biochemistry 86: 307-319, 2002
32. Wyatt CA, Coon CI, Gleeson J and Brinckerhoff CE. Potential for the 2G single nucleotide polymorphism (SNP) in the promoter of Matrix Metalloproteinase (MMP-1) to enhance gene expression in normal stromal cells, Cancer Res. 62: 7200-7202, 2002
33. Brinckerhoff CE and Sporn MB. Retinoids and Rexinoids for the 21st century: a brave new world for arthritis. J. Rheum. 30:211-213, 2003
34. Tower GB, Coon CI, Belguise K, Chalbos D, Brinckerhoff CEFra-1 targets the AP-1 site/2G single nucleotide polymorphism (ETS site) in the MMP-1 promoter. Eur J Biochem. 270:4216-25, 200.
35. Mix KS, Coon CI, Rosen ED, Suh N, Sporn MB and Brinckerhoff CE. PPAR-[gamma)-independent repression of collagenase gene expression by CDDO and 15-dPGJ2: A role for Smad signaling.. Mol. Pharmacol., 65:309-318,2004
36. Huntington JT, Shields JM, Der CJ, Wyatt CA, Benbow U, Slingluff CL and Brinckerhoff CE. Overexpression of collagenase 1 (MMP-1) is mediated by the ERK pathway in invasive melanoma cells: role of BRAF mutation and FGF signaling. J. Biol. Chem. 279: 33168-33176, 2004
37. Mix KS, Sporn MB and Brinckerhoff CE. Novel inhibitors of matrix metalloproteinase gene expression as potential therapies for arthritis. Clinical Orthopaedics and Related Research, 427 (Supple): 129-137,2004.
38. Beehler BC, Brinckerhoff CE and Ostrowski J. Selective retinoic acid receptor ligands for theumatoid arthritis. Curr. Opin. Investig. Drugs 5: 1153-1157, 2004

39. Petrella BL, Lohi J and Brinckerhoff CE. Identification of membrane type-1 matrix metalloproteinase as a target of hypoxia-inducble factor 2alpha in von Hippel-Lindau renal cell carcinoma. Oncogene 24: 1043-1053, 2005
40. Wyatt CW, Geoghegan JC and Brinckerhoff CE**.** Short hairpin RNA mediated inhibition of Matrix Metalloproteinase-1 in MDA-231 cells: effects on matrix destruction and tumor growth .Cancer Research.65: 11101-11108, 2005
41. Burrage PS, Mix KS and Brinckerhoff CE. Matrix metalloproteinases: role in arthritis**.** Front Biosci. 11:529-543, 2006
42. Petrella BL and Brinckerhoff CE. Tumor cell invasion of von Hippel Lindau renal cell carcinoma cells is mediated by membrane type-1 matrix metalloproteinase. Molecular Cancer 5:66-80, 2006
43. Burrage PS, Huntington JT, Sporn MB and Brinckerhoff CE. Regulation of Matrix Metalloproteinase gene expression by an RXR-specific ligand. Arthritis and Rheum. 56: 892-904, 2007
44. Mix KS, Attur M, Al-Mussawir H, Abramson SB, Brinckerhoff CE and Murphy EP. Transcriptional repression of matrix metalloproteinase gene expression by the orphan nuclear receptor NURR1 in cartilage. J. Biol. Chem. 282:9492-9505. 2007
45. Burrage PS and Brinckerhoff CE. Molecular targets in osteoarthritis: metalloproteinases and their inhibitors. Curr. Drug Targets. 8: 293-303, 2007.
46. Vincenti MP and Brinckerhoff CE. Signal transduction and cell-type specific regulation of matrix metalloproteinase gene expression: Can MMPs be good for you?J Cell Physiol. 213:355-364, 2007.
47. Blackburn JS, Rhodes CH, Coon CI and Brinckerhoff CE. RNAi inhibition of MMP-1 prevents melanoma metastasis by reducing tumor collagenase activity and angiogenesis. Cancer Res. 67:10849-10858, 2007
48. Eck, S.M., Hoopes, P.J., Petrella, B.L., Coon, C.I. and Brinckerhoff, C.E. Matrix metalloproteinase-1 promot3es breast cancer angiogenesis and osteolysis in a novel in vivo model. Breast Cancer Res. and Treatment. In press, 2008
49. Blackburn JS and Brinckerhoff CE. Matrix Metalloproteinase-1 (MMP-1) and thrombin differentially activate gene expression in endothelial cells via PAR-1 and promote angiogenesis. In press. Am, J. Pathology, 2008
50. Burrage PS, Schmucker AC, Ren Y, Sporn MB and Brinckerhoff CE. Retinoid X receptor and peroxisome proliferators-activated receptor gamma agonists cooperate to inhibit matrix metalloproteinase gene expression. Arthritis Res Ther. 2008 Dec 1;10(6):R139. [Epub ahead of print]

Current Support

Title: **Regulation of Collagenase Gene Expression**
NIH-NIAMS AR-26599-28
Dates of project: 6/1/2007 – 5/31/2012
The major goals of this project are: (1) Investigate the molecular mechanisms (genetic and epigenetic) by which RXR and PPARg ligands selectively repress MMP-1 and MMP-13 gene expression; (2) Use the PPARg antagonist, GW-9662, to investigate the differential regulation of MMP-1 and MMP-13 gene expression; (3) Test the efficacy of RXR and PPARg ligands in preventing cartilage degradation in a murine model of collagen induced arthritis.

Pending Support

Title: **Invasive Behavior of Tumor Cells Producing Collagenase-1**
NIH-NCI CA-77267-08A2
Specific Aims:
(1). Define effects of the MMP-1/PAR-1 autocrine signaling axis in the RGP to VGP transition, and in the metastatic phenotype of VGP melanomas; (2). Define effects of the MMP-1/PAR-1 paracrine signaling axis on endothelial cells by VGP melanomas.(3) Investigate the mechanisms by which MMP-1 facilitates tumor growth at metastatic sites *in vivo*.