BIOGRAPHICAL SKETCH

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NAME: QUIGLEY, JAMES P.

eRA COMMONS USER NAME (agency login): JQUIGLEY

POSITION TITLE: Professor, Dept of Cell and Molecular Biology

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Manhattan College, New York City, NY	BS	06/1965	Chemistry
Johns Hopkins University School of Medicine, Baltimore, MD	PHD	06/1970	Physiological Chemistry
The Rockefeller University, New York, NY	Postdoctoral Fellow	06/1973	Tumor Cell Biochemistry

A. Personal Statement

I have had long standing interest in the process of tumor progression and the molecules that contribute to it, particularly as they relate to malignant dissemination and tissue colonization. The types of molecules that have received most of my attention over the past 30 years include various proteolytic enzymes, their inhibitors, substrates and regulators, including members of the serine protease family and members of the MMP family. In addition I also have long term experience in the detection, purification, analysis and characterization of cell surface transmembrane proteins and receptors as they relate to cell function *in vivo*. To lay the groundwork for examining these various types of molecules, my laboratory has been instrumental in developing a significant number of *in vitro* and *in vivo* model systems for the study of these molecules. The model systems that have been developed over the past 10 years have been focused on in vivo live animal models using chick embryos and genetically defined mice. A special emphasis with our models has been placed on quantifying various steps in tumor dissemination including invasion, intravasation, inflammatory cell infiltration, tumor cell survival in tissues, angiogenesis and initial colonization of secondary tissues. A new experimental focus on the critical role of the host vasculature responding to escaping primary tumor cells has also prepared me to conduct this project.

B. Positions and Honors

Positions and Employment

1973 - 1974 Assistant Professor, Dept of Chemical Biology, The Rockefeller University, New York, NY
1974 - 1984 Adjunct Assistant-Associate Professor, The Rockefeller University, New York, NY
1975 - 1982 Assistant / Associate Professor, Dept of Microbiology, SUNY Downstate, Brooklyn, NY
1980 - 1981 Visiting Professor, Oxford University, Sir William Dunn School of Pathology, Oxford, U.K.
1982 - 1987 Professor, Dept of Microbiology & Immunology, SUNY Downstate, Brooklyn, NY
1987 - 1999 Professor, Dept of Pathology, SUNY Stony Brook, Stony Brook, NY
1993 - 1994 Visiting Professor, UCSF Medical Center, San Francisco, CA
1999 - 2001 Professor, Dept of Vascular Biology, The Scripps Research Institute, La Jolla, CA
2001 - Professor, Dept of Cell & Molecular Biology, The Scripps Research Institute, La Jolla, CA

Other Experience and Professional Memberships

- Present Member, American Association of Cancer Research
- Present Member, American Society for Biochemistry & Molecular Biology
- Present Member, American Society for Cell Biology
- Present Member, American Society for Matrix Biology

- Present Member, The Biochemical Society

Honors

1970 - 1972 Leukemia Society of America Fellow at Rockefeller University, Leukemia Society of America
1978 - 1980 Sinsheimer Foundation Scholar at SUNY Downstate, Sinsheimer Foundation
1980 - 1981 Fogarty International Scholar at Oxford University, Fogarty International
1981 - 1986 Member, Cellular Physiology Study Section, NIH
1987 - 1991 Co-Chairman, Biochemistry Study Section, American Cancer Society
1988 - 1990 Catacosinos Cancer Research Professorship at SUNY Stony Brook
1992 - 1996 Member, Pathobiochemistry (PBC) Study Section, NIH
1996 - 2006 Editorial Board, The Journal of Biological Chemistry
2000 - Present Ad Hoc Member, TPM and TME Study Sections, NIH/NCI
2009 - Present Editorial Board, The Journal of Biological Chemistry

C. Contribution to Science

1. A significant part of the research in my laboratory over the past 35+ years has been characterizing the involvement of proteolytic enzymes in the phenotypic behavior of highly-malignant cells. Our focus has been on the members of the serine protease family, particularly uPA and plasmin and select members of the MMP family, particularly MMP-2 and MMP-9 and recently MMP-1. My lab was the first to show that uPA itself when expressed by highly-malignant cells can catalytically act independent of its natural target substrate, plasminogen and alter the phenotype of the transformed cells. We generated unique anti-catalytic monoclonal antibodies to uPA to confirm this novel activity. We also first demonstrated distinct cross-over cascade reactions that merged the activation of MMP zymogens with the uPA/plasmin cascade to facilitate tumor invasion. More recent work has demonstrated that uPA-generated plasmin can cleave select transmembrane proteins to enhance tumor cell survival. We also have demonstrated that neutrophil MMP-9 is a unique and potent activator of angiogenesis.

    a. **Quigley JP**. Phorbol ester-induced morphological changes in transformed chick fibroblasts: evidence for direct catalytic involvement of plasminogen activator. Cell. 1979 May;17(1):131-41. PubMed PMID: 222474.
    b. Sullivan LM, **Quigley JP**. An anticatalytic monoclonal antibody to avian plasminogen activator: its effect on behavior of RSV-transformed chick fibroblasts. Cell. 1986 Jun 20;45(6):905-15. PubMed PMID: 3011282.
    c. Ramos-DeSimone N, Hahn-Dantona E, Sipley J, Nagase H, French DL, **Quigley JP**. Activation of matrix metalloproteinase-9 (MMP-9) via a converging plasmin/stromelysin-1 cascade enhances tumor cell invasion. J Biol Chem. 1999 May 7;274(19):13066-76. PubMed PMID: 10224058.
    d. Casar B, Rimann I, Kato H, Shattil SJ, **Quigley JP**, Deryugina EI. In vivo cleaved CDCP1 promotes early tumor dissemination via complexing with activated β1 integrin and induction of FAK/PI3K/Akt motility signaling. Oncogene. 2014 Jan 9;33(2):255-68. PubMed PMID: 23208492; PubMed Central PMCID: PMC3931462.

2. My laboratory over many years has been active in using immunological and proteomic methods to identify cell surface transmembrane proteins that function in metastatic dissemination. We first used a novel, unbiased approach termed Subtractive Immunization (S.I.) to generate monoclonal antibodies (mAbs) that react with transmembrane proteins that are enriched on the surface of highly metastatic human tumor cells over that of isogenic non-metastatic variant cells. We devised *in vivo* models to screen these selected mAbs for their ability to block or inhibit metastasis, and then employed immuno-proteomics to identify the mAb's target antigen. With these unique function-blocking mAbs we identified several new cell surface proteins that turned out to be important contributors to tumor progression, including a new tetraspanin (CD151) and the first member of the CUB Domain Containing Protein family, CDCP-1. We went on to demonstrate that CDCP-1 becomes highly phosphorylated and signals for enhanced tumor cell survival, suggesting its role in metastatic dissemination. With these solid background studies on metastasis-blocking approaches, we are well qualified to contribute to the present proposal.

a. Brooks PC, Lin JM, French DL, **Quigley JP**. Subtractive immunization yields monoclonal antibodies that specifically inhibit metastasis. J Cell Biol. 1993 Sep;122(6):1351-9. PubMed PMID: 8376467; PubMed Central PMCID: PMC2119848.

b. Hooper JD, Zijlstra A, Aimes RT, Liang H, Claassen GF, Tarin D, Testa JE, **Quigley JP**. Subtractive immunization using highly metastatic human tumor cells identifies SIMA135/CDCP1, a 135 kDa cell surface phosphorylated glycoprotein antigen. Oncogene. 2003 Mar 27;22(12):1783-94. PubMed PMID: 12660814.

c. Zijlstra A, Lewis J, Degryse B, Stuhlmann H, **Quigley JP**. The inhibition of tumor cell intravasation and subsequent metastasis via regulation of in vivo tumor cell motility by the tetraspanin CD151. Cancer Cell. 2008 Mar;13(3):221-34. PubMed PMID: 18328426; PubMed Central PMCID: PMC3068919.

d. Casar B, He Y, Iconomou M, Hooper JD, **Quigley JP**, Deryugina EI. Blocking of CDCP1 cleavage in vivo prevents Akt-dependent survival and inhibits metastatic colonization through PARP1-mediated apoptosis of cancer cells. Oncogene. 2012 Aug 30;31(35):3924-38. PubMed PMID: 22179830; PubMed Central PMCID: PMC4350937.

3. For the past 20 years and right up to the present, our laboratory has been developing and modifying *in vivo* model systems to study and also quantify various processes in tumor progression including but not limited to angiogenesis, tumor invasion, cancer cell survival and metastasis. Beginning when we first reviewed, analyzed and then utilized human specific *alu* repeat qPCR to monitor the extent of human tumor cell dissemination in xenographic animal models, we have made significant advancements in quantifying various aspects of tumor progression. We also have utilized this qPCR-based method in tandem with various *in vivo* tumor implantation models to select out human tumor carcinoma variants that differ in their metastatic capabilities 10-100 fold. We are utilizing these same quantitative *in vivo* approaches in the current proposal.

   a. **Quigley JP**, Armstrong PB. Tumor cell intravasation alu-cidated: the chick embryo opens the window. Cell. 1998 Aug 7;94(3):281-4. PubMed PMID: 9708729.

   b. Deryugina EI, **Quigley JP**. Chick embryo chorioallantoic membrane model systems to study and visualize human tumor cell metastasis. Histochem Cell Biol. 2008 Dec;130(6):1119-30. PubMed PMID: 19005674; PubMed Central PMCID: PMC2699943.

   c. Conn EM, Botkjaer KA, Kupriyanova TA, Andreasen PA, Deryugina EI, **Quigley JP**. Comparative analysis of metastasis variants derived from human prostate carcinoma cells: roles in intravasation of VEGF-mediated angiogenesis and uPA-mediated invasion. Am J Pathol. 2009 Oct;175(4):1638-52. PubMed PMID: 19729488; PubMed Central PMCID: PMC2751560.

   d. Juncker-Jensen A, Deryugina EI, Rimann I, Zajac E, Kupriyanova TA, Engelholm LH, **Quigley JP**. Tumor MMP-1 activates endothelial PAR1 to facilitate vascular intravasation and metastatic dissemination. Cancer Res. 2013 Jul 15;73(14):4196-211. PubMed PMID: 23687338; PubMed Central PMCID: PMC3754905.

4. Our laboratory has also been active in studying angiogenesis and tumor cell-vascular interactions, especially as they relate to proteases (uPA, MMP-9), growth factors (VEGF, FGF, TGFB) and cytokines (IL-8), all of which are under current investigation. We were the first to demonstrate the biochemical reason why proMMP-9 derived from inflammatory neutrophils is such a potent angiogenic factor, namely because it is produced by these cells in a unique TIMP-1-free form that is rapidly and readily activated. We have recently demonstrated that IL-8-induced neutrophil influx into the tumor microenvironment is the basis for the major MMP-9 induced angiogenic switching.

   a. Seandel M, Noack-Kunnmann K, Zhu D, Aimes RT, **Quigley JP**. Growth factor-induced angiogenesis in vivo requires specific cleavage of fibrillar type I collagen. Blood. 2001 Apr 15;97(8):2323-32. PubMed PMID: 11290594.

   b. Ardi VC, Van den Steen PE, Opdenakker G, Schweighofer B, Deryugina EI, **Quigley JP**. Neutrophil MMP-9 proenzyme, unencumbered by TIMP-1, undergoes efficient activation in vivo and catalytically induces angiogenesis via a basic fibroblast growth factor (FGF-2)/FGFR-2 pathway. J Biol Chem. 2009 Sep 18;284(38):25854-66. PubMed PMID: 19608737; PubMed Central PMCID: PMC2757987.

c. Zajac E, Schweighofer B, Kupriyanova TA, Juncker-Jensen A, Minder P, **Quigley JP**, Deryugina EI. Angiogenic capacity of M1- and M2-polarized macrophages is determined by the levels of TIMP-1 complexed with their secreted proMMP-9. Blood. 2013 Dec 12;122(25):4054-67. PubMed PMID: 24174628; PubMed Central PMCID: PMC3862278.

d. Deryugina EI, Zajac E, Juncker-Jensen A, Kupriyanova TA, Welter L, **Quigley JP**. Tissue-infiltrating neutrophils constitute the major in vivo source of angiogenesis-inducing MMP-9 in the tumor microenvironment. Neoplasia. 2014 Oct;16(10):771-88. PubMed PMID: 25379015; PubMed Central PMCID: PMC4212255.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/james.quigley.1/bibliography/40618906/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01 CA105412, National Cancer Institute (NCI) Quigley, James P (PI) 01/16/2004 – 04/30/2020
Transmembrane Proteins Involved in Human Tumor Expansion
Role: PI

The goal of this research proposal is to investigate the molecular mechanisms of proteolytic functional activation of molecules expressed on the cell surface of aggressive tumor cells. Specifically, we will investigate the functional activation of CDCP1 by plasmin and CD44 by MMP-9. It will be determined whether the prevention of proteolytic modification of these molecules could be exploited for therapeutic inhibition of tumor cell dissemination in cancer metastasis models.

R01 CA157792, National Cancer Institute (NCI) Quigley, James P (PI) 09/01/2012 – 06/30/2017
Role of Inflammatory Neutrophils and their Unique MMP-9 in Tumor Progression
Role: PI

The goal of this study is to investigate the functional roles of inflammatory neutrophils in the process of tumor cell intravasation and induction of intravasation-supporting vasculature. Special emphasis is placed on a quantitative comparison of tumor-associated neutrophils *versus* tumor-associated macrophages with regard of the production and delivery of their angiogenesis-inducing TIMP-1-free proMMP-9 at early stages of tumor development and metastasis.

Completed Research Support

R01 CA129484, National Cancer Institute (NCI) Quigley, James P (PI) 08/05/2008 – 05/31/2014
A Cellular and Molecular Analysis of the Intravasation Step in Tumor Metastasis
Role: PI

The goal of this study was to investigate the cell surface molecules and proteolytic enzymes, which are critically important for aggressive cancer cell to accomplish the intravasation step of the metastatic cascade, namely the induction of inflammatory cell response and MMP-9-dependent tumor angiogenesis, maintenance of intravasation-supporting vasculature, dissolution of intercellular contacts within the primary tumor, and proteolytic modifications of tumor microenvironment.