OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

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NAME: Nancy L. Oleinick

eRA COMMONS USER NAME (credential, e.g., agency login): noleinick

POSITION TITLE: Professor of Radiation Oncology, Biochemistry, Oncology (Cancer Center), & Environmental Health Sciences

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

| INSTITUTION AND LOCATION | DEGREE(if applicable) | Completion DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Chatham College, Pittsburgh, PAUniversity of Pittsburgh, Pittsburgh, PA | B.S.Ph.D. | 06/196208/1966 | ChemistryBiochemistry |
| Case Western Reserve University, Cleveland, OH | Post Doc. | 1966-68 | Biochemistry |
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# A. Personal Statement

I am a biochemist who has applied her expertise to study of cellular and molecular mechanisms of novel drugs and radiations and their interaction. Among other contributions, this has led to identification of radiation-induced DNA-protein complexes as targets of polyamine radioprotection in chromatin, elucidation of unique mechanisms for induction of apoptosis by photodamage, and recent findings of enhanced radiosensitization with inhibition of base-excision repair. Along with those efforts, I have worked with interested physicians to advance drugs identified in my research into clinical trials. As clinical studies of one of those drugs, the photosensitizer Pc 4, increased, I became the Chief Scientific Officer of a start-up company to accelerate clinical development. I have recently returned to studies of novel radiosensitizers. I have been recognized for these accomplishments by appointment to multiple NIH study sections and to major national committees examining the effects of radiation, as listed in Section B. Specific scientific contributions mentioned here are highlighted by the following publications. Thus, I am well suited to direct pre-clinical studies of radiation-drug interactions, to collaborate on translational aspects of clinical development of those interactions, to consult on studies of radiation mechanisms and drug development for chemotherapeutics and radiosensitization, and to train students in these areas.

* 1. Chiu SM and Oleinick NL, Radioprotection of cellular chromatin by the polyamines spermine and putrescine: Preferential action against formation of DNA-protein crosslinks, Radiat. Res. 149, 543-549 (1998).
	2. Xue, L. Y., S. M. Chiu, and N. L. Oleinick, Photochemical destruction of the Bcl-2 oncoprotein during photodynamic therapy with the phthalocyanine photosensitizer Pc 4. Oncogene 20: 3420-3427 (2001).
	3. Kinsella, T.J., E.D. Baron, V.C. Colussi, K.D. Cooper, C.L. Hoppel, S.T. Ingalls, M.E. Kenney, X. Li, N.L. Oleinick, S.R. Stevens, and S.C. Remick, Preliminary clinical and pharmacologic investigation of photodynamic therapy with the silicon phthalocyanine photosensitizer Pc 4 for primary or metastatic skin cancer. Frontiers Radiat. Onc. (2011) Jun 30;1:14. doi: 10.3389 PMCID: PMC3355859

**B. Positions and Honors**

**Positions and Employment**

1969-76 Assistant Professor, Radiology & Biochemistry (SOM) & School of Dentistry (1971-76), CWRU

1978 Visiting Professor, Dept. of Biological Chemistry, The Hebrew University of Jerusalem, Israel

1976-85 Associate Professor, Radiology and Biochemistry (SOM) and School of Dentistry, CWRU

1986-98 Director, Division of Radiation Biology, Department of Radiology, CWRU

1985- Professor of Radiology (Radiation Oncology as of 1998), Environmental Health Sciences,

 Biochemistry, and Oncology (1987-) (SOM), and Oral Biology (Dentistry, 1985-1991), CWRU

1986-2012 Co-Director, Cell Death Regulation Program, Case Comprehensive Cancer Center

1986-2013 Director, Radiation Resources Core Facility, Case Comprehensive Cancer Center (2013-15, Co-Director)

**Other Experience and Professional Memberships**

1979-82 and 1985-86 Associate Editor, *Radiation Research*

1984-88 Member, Radiation Study Section, NIH

1986-91 Editorial Board, *International Journal of Radiation Biology*

1987-94 Member, CIRRPC Task Force on Neutron Radiobiology

1991-95 Member, Board of Scientific Counselors, Div. of Cancer Etiology, National Cancer Institute

1992-98 Editorial Board, *Photochemistry and Photobiology*

1994-95 Member, Presidential Advisory Committee on Human Radiation Experiments

1996-98 Member, Committee on Health Risks of Exposure to Low Levels of Ionizing Radiation (BEIR VII)

 Phase I, National Research Council

1997-2011 Member, Veterans Advisory Committee on Environmental Hazards

1997-99 President-Elect and President, American Society for Photobiology

* 1. Member, NCI Cancer Manpower and Training Subcommittee (IRG-F); Chair (1999-2002 )

2003 Member, Panel E, Biophysics, Imaging & Radiobiology, NCI of Canada

2004-2007 Member, NCI Parent Committee for Clinical Program Projects (Subcommittee D)

2008-2012 Member, Radiation Therapy and Biology (RTB) Study Section, NIH

2010-present Chief Scientific Officer, Fluence Therapeutics, Inc. (part-time)

**Honors**

1989-1998 NIH MERIT award, National Cancer Institute

2002-present Joseph T. Wearn, M.D., University Professor of Medicine, CWRU

2010 John Yuhas Memorial Lecture Awardee, University of Pennsylvania

# C. Contribution to Science

1. My early research was in basic biochemistry, first as a graduate student studying allosteric factors controlling the activity of the Δ5-3-ketosteroid isomerase, and then as a post-doctoral fellow, the mechanism for the inhibition of bacterial translation by erythromycin. The former demonstrated allosteric promotion of enzyme activity by NAD and NADH. The latter demonstrated specific binding sites for erythromycin on the large bacterial ribosomal subunit, an explanation of resistance to this antibiotic.
	1. Oleinick NL and Koritz SB, The activation of Δ5-3-ketosteroid isomerase in rat adrenal small particles by diphosphopyridine nucleotides, Biochemistry 5, 715-724 (1966).
	2. Oleinick NL and Koritz SB, The response of the microsomal Δ5-3-ketosteroid isomerase from several steroidogenic tissues to nicotinamide adenine dinucleotides, Biochim. Biophys. Acta 122, 333-340 (1966).
	3. Oleinick NL and Koritz SB, Studies on the mechanism of the Δ5-3-ketosteroid isomerase from rat adrenal small particles, Biochemistry 5, 3400-3405 (1966).
	4. Oleinick NL and Corcoran JW, Two Types of Binding of Erythromycin to Ribosomes from Antibiotic-sensitive and -resistant Bacillus subtilis 168, J. Biol. Chem. 244, 727-735 (1969).
2. As an independent investigator in the Division of Radiation Biology of the Department of Radiology, I applied my expertise in biochemistry and mechanisms of protein synthesis to questions of interest at the time, such as the control of the radiation-induced delay of mitosis, which is now known to result from stalling of cell cycle progression at the G2 checkpoint, and the influence of chromatin structure on the sensitivity of DNA to ionizing radiation. My laboratory was the first to demonstrate hypersensitivity of active chromatin to radiation damage and the cross-linking of nuclear matrix proteins by radiation.
	1. Chiu SM, Oleinick NL, Friedman LR, and Stambrook PJ, Hypersensitivity of DNA in transcriptionally active chromatin to ionizing radiation, Biochim. Biophys. Acta 699, 15-21 (1982).
	2. Ramakrishnan N, Chiu SM, and Oleinick NL, Yield of DNA-protein cross-links in γ-irradiated Chinese hamster cells, Cancer Res. 47, 2032-2035 (1987).
	3. Chiu SM, Xue LY, Friedman LR, and Oleinick NL, Copper-ion-mediated sensitization of nuclear matrix attachment sites to ionizing radiation. Biochemistry 32, 6214-6219 (1993).
	4. Balasubramaniam U and Oleinick NL, Preferential crosslinking of matrix-attachment region (MAR)­containing DNA fragments to the isolated nuclear matrix by ionizing radiation, Biochemistry 34, 12790-­12802 (1995).
3. As my interest in photodynamic therapy (PDT) grew, I organized and led a multi-disciplinary team of investigators to design and synthesize new and better photosensitizers for PDT, to decipher the mechanism of cell death with the best of these photosensitizers, and to optimize their use in animal models as a precursor for eventual clinical trials. My lab identified one of those photosensitizers, the phthalocyanine Pc 4, as a powerful light-activated drug with virtually no activity in the dark. I was the first to demonstrate that apoptosis was the major response to PDT with Pc 4 and other photosensitizers that accumulate in mitochondria. I then deciphered the unique mechanism for induction of apoptosis by PDT with mitochondrion-targeting phthalocyanine photosensitizers, *i.e*., specifically generating photodamage to the anti-apoptotic proteins Bcl-2 and Bcl-xL and demonstrated different mechanisms for lysosome-targeting photosensitizers. These findings changed the way investigators understood PDT mechanisms in cells and have been the subject of several reviews, including some I have written.

a. Agarwal, M.L., M.E. Clay, E.J. Harvey, H.H. Evans, A.R. Antunez, and N.L. Oleinick, Photodynamic therapy induces rapid cell death by apoptosis in L5178Y mouse lymphoma cells, Cancer Res. 51, 5993-5996 (1991).

b. Usuda, J., S. M. Chiu, E. Murphy, L. Y. Xue, M. Lam, A. L. Nieminen, and N. L. Oleinick, Domain-dependent photodamage to Bcl-2: a membrane-anchorage region is needed to form the target of phthalocyanine photosensitization. J. Biol. Chem. 278: 2021-2029 (2003)

c. Xue, L.Y., S.M. Chiu, A. Fiebig, D.W. Andrews, and N.L. Oleinick, Photodamage to multiple Bcl-xL isoforms by photodynamic therapy with the phthalocyanine photosensitizer Pc 4. Oncogene 22: 9197-9204 (2003).

d. Rodriguez, M.E., K. Azizuddin, S.M. Chiu, L.Y. Xue, P. Zhang, M. Lam, M.E. Kenney, A.L. Nieminen, and N. L. Oleinick, Structural factors and mechanisms underlying the improved photodynamic cell killing with silicon phthalocyanine photosensitizers directed to lysosomes vs. mitochondria. Photochem. Photobiol. 85: 1189-1200 (2009) PMCID: PMC3351115

1. With collaborators, I demonstrated the strong response of many types of preclinical tumor models to PDT with Pc 4. Following on the preclinical work, my research in PDT expanded into collaborations with physicians to develop PDT with Pc 4 for clinical applications. These studies, led by members of the Departments of Dermatology and Radiation Oncology, demonstrated safety and some efficacy for Pc 4-based PDT in skin cancers, especially cutaneous T-cell lymphoma, and in psoriasis. This clinical application is being pursued by a start-up company, Fluence Therapeutics, LLC, for which I serve as Chief Scientific Officer. In addition to the studies on skin diseases, I am working with a member of the Department of Otolaryngology-Head and Neck Surgery, to complete the regulatory review of a proposed clinical trial of Pc 4-PDT to treat recurrent respiratory papillomatosis, based on excellent data in a preclinical mouse model.
	1. Miller, J.D., E.D. Baron, H. Scull, A. Hsia, J.C. Berlin, T. McCormick, V. Colussi, M.E. Kenney, K.D. Cooper, and N.L. Oleinick, Photodynamic therapy with the phthalocyanine photosensitizer Pc 4: The Case experience with preclinical mechanistic and early clinical-translational studies, Toxicol. Appl. Pharmacol., 224: 290-299 (2007). PMCID: PMC2128784.
	2. Colussi, V.C., D.K. Feyes, J.W. Mulvihill, Y.S. Li, M.E. Kenney, C.A. Elmets, N.L. Oleinick and H. Mukhtar, Phthalocyanine 4 (Pc 4) Photodynamic therapy of human OVCAR-3 tumor xenografts, Photochem. Photobiol. 69, 236-241 (1999).
	3. Lee, R.G., M.A. Vecchiotti, J. Heaphy, A. Panneerselvam, M.D. Schluchter, N.L. Oleinick, P. Lavertu, K.N. Alagramam, J.E. Arnold, and R.C. Sprecher, Photodynamic therapy of cotton-tailed rabbit papilloma virus-induced papillomas in a severe combined immunodeficient mouse xenograft system. Laryngoscope 120(3): 618-624 (2010).
	4. Baron, E.D., C.L. Malbasa, D. Santo-Domingo, J.D. Miller, K. Hanneman, A.H. Hsia, N.L. Oleinick, V.C. Colussi, K.D. Cooper, Silicon phthalocyanine (Pc 4) photodynamic therapy is a safe modality for cutaneous neoplasms: Results of a phase 1 clinical trial. Lasers Surg. Med. 42(10):728-35, 2010. PMCID: PMC3149858
2. In recent years, I have developed a renewed interest in radiosensitization using drugs that are either approved or in development as cancer chemotherapeutics. These efforts have focused on the use of pemetrexed and methoxyamine for radiosensitization of locally advanced lung cancer and new inhibitors of ribonucleotide reductase as radiosensitizers of cervical and head-and-neck cancers. In addition to published work, there are two papers submitted on these topics. The former studies have resulted in a CTEP-approved clinical trial of pemetrexed/methoxyamine/cis-platin/radiation therapy with sequencing of the agents for optimum tumor response as identified in our preclinical studies.
	1. Kunos, C.A., V.C. Colussi, J. Pink, T. Radivoyevitch, and N.L. Oleinick, Radiosensitization of human cervical cancer cells by inhibiting ribonucleotide reductase: Enhanced radiation response at low dose rates. Int. J. Radiat. Oncol. Biol. Phys. 80(4):1198-1204 (2011). PMCID: PMC3118909
	2. Bulgar, AD, L D Weeks, Y Miao, S Yang, Y Xu, C Guo, S Markowitz, N Oleinick, S L Gerson and L Liu, Removal of uracil by uracil DNA glycosylase limits pemetrexed cytotoxicity: overriding the limit with methoxyamine to inhibit base excision repair, Cell Death and Disease (2012) **3**, e252. PMCID: PMC3270269
	3. Perera, R., R. Patel, H. Wu; M. Gangolli; B. Traughber; N. Oleinick, and A.A. Exner. Preclinical evaluation of radiosensitizing activity of Pluronic block copolymers. Int. J. Radiat. Biol. 89(10), 801-812 (2013). PMCID: PMC3962015 \*Article featured on globalmedicaldiscovery.com\*
	4. Ahmad MF, Huff SE, Pink J, Alam I, Zhang A, Perry K, Harris ME, Misko T, Porwal SK, Oleinick NL, Miyagi M, Viswanathan R, Dealwis CG., Identification of non-nucleoside human ribonucleotide reductase modulators. J Med Chem 10/2015; DOI:10.1021/acs.j. PMID: 26488902

**Complete List of Published Work in MyBibliography**:  <http://www.ncbi.nlm.nih.gov/sites/myncbi/nancy.oleinick.1/bibliography/40453486/public/?sort=date&direction=ascending>.

**D. Research Support**

Ongoing Research Support

P30 CA43703-20 (Gerson) 9/30/91-3/31/17

NIH/NCI

Case Comprehensive Cancer Center Support Grant

 This is core support for the Case Comprehensive Cancer Center which operates support facilities for cancer researchers. There is no direct support for research.

Role: Co-Director, Radiation Resources Core Facility

Completed Research Support

1P50AR055508-02 (Cooper) 09/24/07-08/31/12

NIH/NIAMS: Center of Research Translation (CORT) in Psoriasis

This grant supports basic, clinical, and translational research in psoriasis. There are 3 projects and 2 cores.

Project 1 (Baron, Project Director)

Pc 4-PDT for Psoriasis

 This project conducts a Phase I trial for the treatment of psoriasis with topically applied Pc 4 and red light, translational studies of the mechanism of Pc 4-PDT in psoriasis and studies of biomarkers of response.

Role: Co-Investigator