

Natalia Y. Tretyakova

University of Minnesota
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EDUCATION

- 1993 – 1997 Ph.D. University of North Carolina, Chapel Hill, NC, Dept. of Environmental Sciences and Engineering. Thesis: "Identification and quantitation of 1,3-butadiene-induced DNA adducts using mass spectrometry"
- 1985 – 1990 B.S., M.S. in Chemistry, Moscow State University, Moscow, Russia,

WORK EXPERIENCE

- May 2000 – present University of Minnesota, Minneapolis, MN – Department of Medicinal Chemistry and Cancer Center – Assistant Professor
- 1997 – 2000 Massachusetts Institute of Technology, Cambridge, MA – Division of Bioengineering and Environmental Health - Postdoctoral Research Associate

RESEARCH INTERESTS

- the chemistry of DNA damage with exogenous and endogenous carcinogens
- sequence effects on chemical reactivity of DNA nucleobases
- DNA-DNA and DNA-protein cross-linking by antitumor drugs and bifunctional carcinogens

AWARDS

- 2003-2005 McKnight-Land Grant professorship, University of Minnesota
- 1997 Student Award, North Carolina Society of Toxicology
- 1996 Student Award, North Carolina Society of Toxicology
- 1995 Student Travel Award, International Congress of Toxicology, Seattle, WA
- 1995 Student Travel Award, International Symposium on Butadiene and Isoprene Health Risks, Blaine, WA
- 1994 Weiss Award, University of North Carolina
- 1991 Moscow State University Award for Best Works of Young Scientists on Environmental Theme.

PROFESSIONAL MEMBERSHIPS

American Association for Cancer Research
American Chemical Society
American Society for Mass Spectrometry
International Society for Study of Xenobiotics
American Association of the Colleges of Pharmacy

EDITORIAL DUTIES Ad hoc Reviewer for *Chemical Research in Toxicology, Biochemistry Carcinogenesis, Anal. Biochem., J. Med. Chem., J. Am. Soc. Mass Spectrometry, Biochemistry, Nucleic Acids Research*

INVITED LECTURES

51st Annual Conference on Mass Spectrometry and Related Topics, Montreal, Canada, June 8 - 12, 2003: *Probing the reactivity of specific positions within DNA towards carcinogens and drugs by stable isotope labeling HPLC-ESI-MS/MS*

226th National Meeting of the American Chemical Society, New York, NY, Sept. 7-11, 2003
Stable isotope labeling-mass spectrometry to map the reactivity of DNA bases towards carcinogens and antitumor agents

Carleton College, Dept. of Chemistry: Feb 21, 2003: *Mass Spectrometry of Chemically modified DNA*

2nd Engebreston Symposium on Drug design, Mayo Clinic, Sept. 11, 2002 *Sequence Selectivity for DNA Modification with Carcinogens and Drugs*

Mutagenesis and Carcinogenesis Gordon Research Conference March 3 - March 8, 2002, in Ventura, California. *Mapping nucleobase adducts within DNA sequences with electrospray and MALDI mass spectrometry*

34th Great Lakes Regional Meeting of the American Chemical Society June 2-4, 2002
Minneapolis, MN. *Mass Spectrometry of Chemically modified DNA*

Univ. of Minnesota Cancer Center Seminar Series: May 15, 2001 *Mapping carcinogen-induced nucleobase lesions within DNA sequences by mass spectrometry.*

Univ. Of Minnesota Chemical Biology Colloquium: October 17, 2001 *Mass Spectrometry of Chemically Modified DNA*

Minnesota Mass Spectrometry Discussion Group: October 9, 2000 *Mass Spectral Analysis of the Distribution of Carcinogen-modified DNA Nucleobases within DNA Sequences*

PUBLICATIONS

Park, S., Hodge, J., and Tretyakova, N. Molecular mechanisms of bifunctional electrophiles: novel guanine-adenine cross-links of diepoxybutane. *In preparation.*

Balcome, S., Park, S., and Tretyakova, N.: Amino acid adducts and DNA-protein cross-links of antitumor nitrogen mustards. *In preparation.*

Matter, B., Jones, R., Shallop, and Tretyakova, N.Y. formation of diastereomeric

benzo[a]pyrene diol epoxide adducts in *p53* derived DNA sequences: correlation with the mutational spectrum. *In preparation*.

Ziegel, R., Shallop, A., Jones, R., Tretyakova, N. Endogenous 5-methylcytosine protects neighboring guanines from methylation and pyridyloxobutylation by the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). *Submitted*.

Park, S., Seethraman, M., Shallop, A., Jones, R., and Tretyakova, N. Structural characterization of the major DNA-DNA cross-link of 1,2,3,4-diepoxybutane. *Submitted*.

Matter, B., Csallany, A.S., Malejka-Giganti, D., and Tretyakova, N.Y. Quantitative analysis of the oxidative DNA lesions, 2,2-diamino-4-[(2-deoxy- β -D-erithropentofuranosyl)amino]2,5-dihydrooxazol-5-one *in vitro* and *in vivo* by isotope dilution HPLC-ESI-MS/MS. *Submitted*.

Park, S., Seethraman, M., Ogdie, A., Ferguson, D., Shallop, A., Jones, R., and Tretyakova, N.Y. (2002) 3'-Exonuclease resistance of DNA oligodeoxynucleotides containing O⁶-[4-oxo-4-(3-pyridyl)butyl] guanine, *Nucleic Acids Research*, **31**(7), 1984-1994.

Ziegel, R., Shallop, A., Jones, R., and Tretyakova, N.Y. (2002) *Kras* gene sequence effects on the formation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-DNA adducts. *Chemical Research in Toxicology*, **16**(4) 541-550.

Tretyakova, N.Y., Matter, B., Jones, R., Shallop, A. (2002) Formation of benzo[a]pyrene diol epoxide-DNA adducts at specific guanines within *K-ras* and *p53* gene sequences: stable isotope labeling mass spectrometry approach. *Biochemistry*, **41**, 9535-9544.

Pfeifer, G.P., Denissenko, M.F., Olivier, M., **Tretyakova, N.Y.**, Hecht, S.S., and Hainaut, P. (2002) Tobacco smoke carcinogens, DNA damage, and *p53* mutations in smoking-associated cancers. *Oncogene* **21**, 7435-51

Upadhyaya, P., Stirla, S.J., **Tretyakova, N.Y.**, Ziegel, R., Villalta, P.W., Wang, M., and Hecht, S.S. (2002) Identification of adducts produced by the reactions of 4-(acetoxymethylnitrosamino)-1-(3-pyridyl)-1-butanol with deoxyguanosine and DNA. *Chem. Res. Toxicol* 2003; **16**(2); 180-190

Tretyakova, N.Y., Matter, B., Ogdie, A., Wishnok, J.S., and Tannenbaum, S.R. (2001) Locating nucleobase lesions within DNA sequences by MALDI-TOF mass spectral analysis of exonuclease ladders. *Chem Res Toxicol*, **14**, 1058-1070.

Tretyakova, N. Y., Wishnok, J.S., and Tannenbaum, S.R. (2000) Peroxynitrite-induced secondary oxidative lesions at guanine nucleobases: chemical stability and recognition by the Fpg repair enzyme. *Chemical Research in Toxicology*, **13**, 658-664.

Tretyakova, N. Y., Burney, S., Pamir, B., Wishnok, J.S., Dedon, P.C., Wogan, G.N., and

Tannenbaum, S.R. (2000) Peroxynitrite-induced DNA damage in the *supF* gene: correlation with the mutational spectrum. *Mutation Research* **447**, 287-303.

Vatsadze, S.Z., Lebedev, A.T., Zyk, N.V., Zefirov, N.S., Tretyakova, N.Y., Hass, J.R. (2000) Fragmentation of 3,7-dialkyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-ones under electron ionization. *Rapid Commun. Mass Spectrom.* **14**, 1949-1953.

Tretyakova, N. Y., Niles, J., Burney, S., Wishnok, J.S. and Tannenbaum, S.R. (1999) Peroxynitrite-induced reactions of synthetic oligonucleotides containing 8-oxoguanine. *Chemical Research in Toxicology*, **12**, 459-466.

Tretyakova, N. Y., Chiang, S-Y., Walker, V. and Swenberg, J.A. (1998) Quantitative analysis of 1,3-butadiene-induced DNA adducts *in vivo* and *in vitro* using liquid chromatography-electrospray ionization tandem mass spectrometry, *Journal of Mass Spectrometry* **33**, 363-376.

Tretyakova, N. Y., Sangaiah, R., Yen, T-Y. and Swenberg, J.A. (1997) Synthesis, characterization and *in vitro* quantitation of N-7-guanine adducts of diepoxybutane. *Chemical Research in Toxicology* **10**, 779-785.

Tretyakova, N.Y., Lin, Y-P, Sangaiah, R., Upton, P.B. and Swenberg, J.A. (1997) Identification and quantification of DNA adducts from calf thymus DNA exposed to 3,4-epoxy-1-butene. *Carcinogenesis* **18**, 137-147.

Tretyakova, N. Y., Sangaiah, R., Yen, T-Y. and Swenberg, J.A. (1997) Adenine adducts with diepoxybutane: isolation and analysis in exposed calf thymus DNA. *Chemical Research in Toxicology* **10**,

Tretyakova, N.Y., Hass, J.R., Saginova, L.G. and Lebedev, A.T. (1997) Decomposition of 3,5-diaryl-oxathiolane-2-oxides under the electron impact. *International Journal of Mass Spectrometry and Ion Processes* **165/166**, 595-607.

Tretyakova, N. Y., Lin, Y-P, Upton, P.B., Sangaiah, R. and Swenberg, J.A. (1996) Macromolecular adducts of butadiene. *Toxicology* **113**, 70-76.

Tretyakova, N.Y., Lebedev, A.T. and Petrosyan, V.S. (1994) Degradative pathways of the aqueous chlorination of orcinol. *Environmental Science and Technology* **28**, 606-613.

Swenberg, J.A., Ham, A., Koc, H., Morinello, E., Ranasinghe, A., **Tretyakova, N.**, Upton, P.B., Wu, K.Y. (2000) DNA adducts: effects of low exposure to ethylene oxide, vinyl chloride and butadiene. *Mutation Research* **464**, 77-86

Koc, H., **Tretyakova, N.Y.**, Walker, V.E., Henderson, R.F., and Swenberg, J.A. (1999) Molecular dosimetry of N-7-guanine adduct formation in mice and rats exposed to 1,3-butadiene. *Chemical Research in Toxicology* **12**, 566-574.

Sangaiah, R., Christova-Georgieva, N.I., Ranasighe, A., **Tretyakova, N.Y.**, Gold, A., Ball, L.M., and Swenberg, J.A. (1997) Synthesis of perdeuterated analogues of the epoxide metabolites of butadiene: 1,2-epoxybut-3-ene-d₆ and 1,2,3,4-diepoxybutane-d₆. *Journal of Labeled Compounds and Radiopharmaceuticals* **39**, 731-739.

Lebedev, A.T., Karakhanova, N.K., Sipyaguin, A.M., Efremov, I.V., **Tretyakova, N.Y.** and Hass, J.R. (1997) Comparative study of the cyclization of dithiocarbamate derivatives of polyhalopyridines induced by electron impact and carried out in solution. *Journal of Mass Spectrometry* **32**, 728-738.

Lebedev, A.T., Predein, E., Bakulev, V., **Tretyakova, N.Y.**, Hass, J.R. (1997) Isomerization of thioamidomethylpyridine ylides and isoquinoline ylides under electron impact. *European Mass Spectrometry* **3**, 217-223.

ABSTRACTS

Ziegel, B. and Tretyakova, N. **Effects of gene sequence and endogenous methylation on DNA adduct formation by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).** Poster presentation at the 94th annual meeting of the American Association for Cancer Research July 2003, Washington, D.C.

Ziegel, B. and Tretyakova, N. **Effects of gene sequence and endogenous methylation on DNA adduct formation by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).** Poster presentation at the annual MIKI meeting, 2003

Park, S. and Tretyakova, N. **Structural characterization and quantitative analysis of 1,2,3,4-diepoxybutane-induced DNA-DNA cross-links.** Poster presentation at the 51st annual meeting of the American Society for Mass Spectrometry: Montreal, Canada June 8 - 12, 2003

Matter, B. and Tretyakova, N. Effects of DNA sequence and cytosine methylation on BPDE-dG adduct formation: Annual symposium **Merging Chemistry & Biology: Perspectives, Progress, and Innovations**, University of Minnesota, May 28, 2003

Tretyakova, N.Y., Matter, B., and Ziegel, R. **Tobacco carcinogen-DNA adduct formation at specific sites within *K-ras* and *p53* gene sequences.** Oral and poster presentation at the National Meeting of the American Chemical Society, August 18-22, 2002, Boston, MA

Park, S. and Tretyakova, N.Y. **DNA-DNA cross-links of 1,3-diepoxybutane.** 2nd Engbretson Symposium. Mayo Clinic: September 11, 2002

Ziegel, B. and Tretyakova, N. **The distribution of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) – DNA-DNA adducts within *K-ras* and *p53* gene sequences.** 2nd

Engebretson Symposium. Mayo Clinic: September 11, 2002

Tretyakova, N.Y., Matter, B., Steele, T. **The distribution of nucleobase lesions within the *K-ras* and *p53* sequences following their treatment with activated tobacco carcinogens.** Paper presented at the 92nd Annual Meeting of the American Society for Cancer Research. New Orleans, LA, March 24-28, 2001

Tretyakova, N.Y., Wishnok, J.S., and Tannenbaum, S.R. **MALDI-TOF MS sequencing of oligonucleotides containing oxidative lesions.** Paper presented at the 48th ASMS conference on Mass Spectrometry and Allied Topics. Long Beach, CA, June 11-15, 2000.

Tretyakova, N.Y., Niles, J., Wishnok, J.S., and Tannenbaum, S.R. **Markers of peroxynitrite exposure in DNA.** Paper presented at the 1999 Sanibel Conference on Clinical Applications of Mass Spectrometry. Jan. 23-27, 1999, Sanibel Island, FL

Tretyakova, N.Y., Niles, J., Burney, S., Wishnok, J.S., Tannenbaum, S.R. **Peroxynitrite-induced DNA damage in the *supF* gene.** Paper presented at the 216th American Chemical Society Meeting. Boston, MA, Aug. 23-27, 1998.

Tretyakova, N.Y., Niles, J., Burney, S., Wishnok, J.S., Tannenbaum, S.R. **HPLC-ESI MS of oligonucleotides modified with peroxynitrite.** Paper presented at the 46th ASMS conference on Mass Spectrometry and Allied Topics. Orlando, FL, June 1-4, 1998.

Tretyakova, N.Y., Hass, J.R. and Swenberg, J.A. **LC-ESI MS/MS in analysis of 1,3-butadiene-induced DNA adducts.** Oral presentation at the 14th Montreux LC-MS Symposium. Cornell University, Ithaca, NY, July 21-25, 1997.

Tretyakova, N.Y., Hass, J.R. and Swenberg, J.A. **LC-ESI MS/MS for identification and quantitation of 1,3-butadiene-induced DNA adducts *in vitro* and *in vivo*.** Oral presentation at the 45th ASMS conference on Mass Spectrometry and Allied Topics. Palm Springs, CA, June 1-5, 1997.

Tretyakova, N.Y., Chiang, S-Y., Walker, V., Hass, J.R. and Swenberg, J.A. **DNA adducts in TK6 cells and tissues of rats and mice exposed to 1,3-butadiene and its metabolites.** Paper presented at the 88th annual meeting of the American Association for Cancer Research. April 12-16, 1997, San Diego, CA.

Tretyakova, N.Y., Hass, J.R., Swenberg, J.A. **Quantification of 1,3-butadiene-induced DNA adducts *in vitro* and *in vivo* using LC-MS/MS.** Paper presented at the 44th ASMS Conference on Mass Spectrometry and Allied Topics. May 12-16, 1996, Portland, OR

Tretyakova, N.Y., Lebedev, A.T., Hass, J.R. **Ortho-cyclization of substituted arylcyclopropanes in gas and liquid phases.** Paper presented at the 44th ASMS Conference on Mass Spectrometry and Allied Topics. May 12-16, 1996, Portland, OR

Tretyakova, N.Y., Bartolotti, L.J., McKinney, J.D., and Christman, R.F. **A density-functional theoretical study of hydrogen abstraction.** *Abstr. Pap. Am. Chem. Soc.* **209**:62-COMP Part 1 Apr. 2 1995

Tretyakova, N.Y., Vatzadze, S., Lebedev, A.T., Zyk, N., Zefirov, N., Hass, J.R. **Fragmentation of 3,7-dialkyl-1, 5-diphenylbispidones under electron impact.** Paper presented at the 43rd ASMS Conference on Mass Spectrometry and Allied Topics. May 21-26, 1995, Atlanta, GA

Tretyakova, N.Y., Hass, J.R., Predein, E., Bakulev, V., Lebedev, A.T. **Isomerization of isoquinoline ylides and thioamidemethylpyridine ylides: the correlation of gas phase and solution rearrangements.** Paper presented at the 13th International Mass spectrometry Conference. August 29 - September 2, 1994, Budapest, Hungary

Tretyakova, N.Y., Lebedev, A.T., Petrosyan, V.S., Christman, R.F., **Mechanisms of the formation of MX-like products from aqueous chlorination of m-dihydroxybenzenes.** Oral presentation at the 206th ACS National Meeting, Chicago, IL, August 22-27, 1993

TEACHING

Biochemistry of Medicinals I (Nucleic Acids), 2001-current
Biochemistry of Medicinals II (Nucleotide Biosynthesis), 2001-current
Chemical Aspects of Drug Metabolism and Bioactivation, 2002-current
Molecular Biology of Cancer, 2003-current
Pharm. D. Paper/Seminar class – Course co-director, 2000-2001
Vistas in Medicinal Chemistry Research, 2001-current
Chemistry of Nucleic Acids – Selected lectures

Supervision of undergraduate students:

Jason Buccek (chemistry) – summer 2000
Shital Sheth (bioengineering)– summer 2000 – fall 2001
Alexis Ogdie (chemistry)– fall 2000-spring 2002
Anthony Frattalone (life sciences program) – summer 2001
Nicole Iverson (chemistry) – summer 2001
Angela Bealka (chemistry) – spring 2002
Michael Walker (chemistry) – spring-fall 2002
Juliya Fisher (Pharmacy) – summer 2002
Christie Burgers (Pharmacy) – fall 2002 – present
Robyn Hoffmeister (Chemistry)– fall 2002 – present
Jake Hodge (Chemistry) – Spring 2003 – present
Lucy Hafner (Pharmacy) – Summer 2003

Supervision of graduate students:

Terry Steele – fall 2000 (9 week rotation)
Rebecca Ziegel – fall 2000-present (thesis advisor)

Ding Lu – fall 2001 (9 week rotation)
Brady Cudd – fall 2002 (9 week rotation)
Mahadevan Seetharaman – spring 2001-spring 2003 (thesis co-advisor)

Postdoctoral Associates:

Soobong Park - fall 2001 – present
Mathur Rajesh – spring 2003-present

COMMITTEES

Department of Medicinal Chemistry Committee for revising the annual evaluation criteria for merit salary increases – Fall 2000
Faculty Search Committee, Dept. of Medicinal Chemistry – Fall 2000 – Spring 2001
Faculty Search Committee – Biochemistry position for Duluth expansion, Fall 2002
Graduate Admissions Committee – Fall 2002 – present
Student Recruitment Committee – Fall 2002 - present

Ph.D. Committee member (2001 – 2002)

Hansen Wang
Zhijun Guo
Bhooma Raghavan
Erik Jorvig
John Goodell
Mahadevan Seetharaman
Vytautas Raulinaitis

RESEARCH SUPPORT

ONGOING

(PI: Tretyakova, N) 04/01/2003 – 03/31/2007 \$142,000 per year
NIH
“DNA cross-linking by diepoxybutane”
This project investigates the structures and biochemical properties of DNA-DNA cross-links induced by diepoxybutane.

(PI: Tretyakova, N) 12/01/2002 – 11/30/2006 \$150,000 per year
NIH
“Sequence distribution of tobacco carcinogen-DNA adducts”
This project will use a recently developed mass spectrometry based approach to analyze the formation of tobacco carcinogen-DNA adducts at specific sites within two critical genes for lung cancer, *p53* and *K-ras*.

(PI: Tretyakova, N) 07/01/2002 – 06/30/2004 \$60,000

Leukemia Research Foundation

“DNA-DNA and DNA-protein cross-linking by antitumor nitrogen mustards”

(PI: Tretyakova, N.) 07/01/03 – 6/30/04 \$30,000

"Capillary HPLC-Triple Quadrupole mass spectrometer"

This grants provides partial funding for the purchase of departmental HPLC-MS/MS instrument.

COMPLETED

(PI: Tretyakova, N) 02/01/2002 – 01/31/2003 \$15,000

Minnesota Medical Foundation

“New Biomarkers of Oxidative Stress and Their Use in Breast Cancer Research”

In this project, new biomarkers of oxidative stress are developed and tested in nitrofluorene-induced rat mammary tumors.

(PI: Tretyakova, N) 07/01/2001 – 06/30/2003 \$52,179

University of Minnesota Cancer Center

“Mechanism-based biomarkers of lung cancer risk in smokers”

This project focuses on the development of biomarkers of lung cancer risk using ultrasensitive capillary HPLC-ESI-MS/MS methodology.

(PI: Tretyakova, N and Ferguson, D.) 07/01/2001 – 07/01/2002 \$25,000

Academic Health Center, University of Minnesota Seed Grant

“Structure-function studies of carcinogen DNA-nitrosamine adducts”

In this project, the role of pyridyloxobutylated DNA adducts of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)

in modulating nuclease activity is studied using a combination of molecular modeling and experimental methods.

1003-652-5964 (PI: Tretyakova, N.) 01/01/2001 – 06/30/2002 \$18,000

Grant-in Aid from the University of Minnesota Graduate School

“Sequence distribution of NNK-induced DNA adducts”

The goal of this research is to develop analytical methodology for analysis of NNK-induced nucleobase lesions.

P50 DA13333 (PI: Tretyakova, N) 09/01/2000 – 09/01/2001 \$10,000

NIDA/NIH

“Identification of target compounds for chemoprevention of lung cancer in smokers”

The goal of this project was to identify tobacco carcinogens to be targeted in chemoprevention of lung cancer.

IRG-58-001-43-08 (PI: Tretyakova, N) 01/01/2001 – 12/31/2001 \$25,000

American Cancer Society Institutional Research Grant to the University of Minnesota

“New methods for mapping tobacco carcinogen-induced nucleobase lesions within DNA”

The major goal of this research was to develop new bioanalytical methods for analysis of carcinogen-DNA adducts within DNA sequences.

3056-9227-01 (PI: Tretyakova, N) 01/01/2001 – 12/31/2001 \$8,784

Minnesota Medical Foundation Faculty Research Grant

“Sequence effects on the distribution of DNA lesions induced by tobacco carcinogens”

This project used mass spectrometry-based approach to map tobacco carcinogen-DNA adducts within critical genes for lung cancer.

(PI: Zimmerman, C) 06/01/2001 – 05/31/2002 \$15,000

University of Minnesota Cancer Center Brainstorm Award

“Role of the small intestine in PhIP activation”

This project investigated the metabolic activation and deactivation of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in small intestine.

OTHER ACTIVITIES

Host for the following seminal speakers:

John Essigmann (MIT)

Nicholas Geacintov (New York University)

JoAnn Stubbe (MIT)

Jim Swenberg (UNC)

Active Collaborations:

Prof. A. Csallany, (Nutrition) – Lipid peroxidation and DNA damage

Prof. Colin Campbell (Pharmacology) – repair of DNA cross-links

Prof. Rick Wagner (Medicinal Chemistry) – activation of phosphoramidate prodrugs

Prof. Karin Musier-Forsyth (Chemistry) – substrate recognition by tRNA synthetases

Prof. D. Malejka-Giganti (VA Hospital) – oxidative DNA damage in breast cancer