BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Barry Gold

eRA COMMONS USER NAME: gold.barry

POSITION TITLE: Professor, Department of Pharmaceutical 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 Date MM/YYYY	FIELD OF STUDY
Hunter College, City University of NY, NY	A.B.	06/66	chemistry
University of Nebraska – Lincoln, NE	Ph.D.	01/72	organic chemistry
University of Toronto, CANADA	Lecturer	09/71-08/73	organic chemistry
University of Nebraska Medical Center, NE	Post-doctorate	09/73-06/76	carcinogenesis

A. Personal Statement: While I was originally trained as an organic chemist, I have been involved in the field of chemical carcinogenesis since 1976 when I took a position at the Eppley Institute for Research in Cancer at the University of Nebraska Medical Center (UNMC). My early training included *in vitro* and *in vivo* metabolism of potential carcinogens and chronic bioassays of chemical carcinogens in rodent species (mice, rats and hamsters). Accordingly, I have been interested in the relationship between exposure to genotoxic chemicals and cancer for my entire career. While chemicals in our environment are associated with a higher risk of cancer, for example the higher incidence of colorectal cancer in diets with grilled meats, normal exposure to DNA damaging agents in many animal models is not sufficient to develop cancer. For this reason, we have turned to the interaction between inflammation and chemical-induced mutagenesis and carcinogenesis. Recently we have adapted, and published, an enzymatic approach to measure stem cell mutations formed in the colon of mice treated with putative promutagenic/carcinogenic compounds. This approach has allowed us to determine whether compound(s) or treatments can generate stem cell mutations or affect the spontaneous mutation frequency presumably due to replication errors and endogenous genotoxins. We have demonstrated that inflammation induced by dextran sulfate sodium does not produce stem cell mutations proving that inflammation associated reactive oxygen/nitrogen species (RONS) are not acting via direct mutagenesis. The current grant application builds and expands on this finding using a mutagen found in grilled meats, which has been epidemiologically tied to human colorectal cancer and is known to produce colon tumors in animal models. We are proposing a novel mechanism by which RONS mediated oxidation converts the initial heterocyclic aromatic amine DNA adduct into more potent promutagenic ring-opened lesions. The analytical MS work is being conducted with my co-investigator (Robert Turesky), who is an established expert in the field of adduct analysis. We have known each other for many years and are excited to collaborate on a project of mutual interest. The proposal was developed based on extensive face-to-face and electronic meetings.

Relevant Publications: (**a**) Whetstone R & Gold B. T-Cells Enhance Stem Cell Mutagenesis in the Mouse Colon. *Mutat. Res.* **744**, 1-5 (2015)(PMID: 25770826)*;* (**b**) Whetstone R & Gold B. (2015) Quantification of glucose-6-phosphate dehydrogenase mutations in colonic stem cells. *J. Vis. Exp., PMID: 26436534;* (**c**) Whetstone W, Wittel U, Michels N, Gulizia JA & Gold B. (2015) Colon carcinogenesis in wild type and immune compromised mice after treatment with azoxymethane, and azoxymethane with dextran sulfate sodium. *Mol. Carcinog*. (PMID: 26153082).

B. Positions and Honors

- Asst. Prof., Eppley Institute for Research in Cancer (Eppley), U. Nebraska Med. Ctr. (UNMC)	1976 - 1981
- Associate Professor (tenured), Eppley & Dept. Pharmaceutical Sciences, UNMC	1981 - 1987
- American Cancer Society Scholar in Cancer Research, Dept. Chemistry, U. of Virginia	1986 - 1987
- Professor, Eppley &, Depts. of Pharmaceutical Sciences, and Biochemistry, UNMC	1988 - 2005
- Associate Director for Basic Research, NCI-designated UNMC Eppley Cancer Center	1993 - 2005
- Associate Director, Eppley Institute for Research in Cancer, UNMC	1994 - 2005
- Interim Director, Eppley Institute for Research in Cancer, UNMC	1997 - 1999
- Professor (tenured) and Chair, Dept. Pharmaceutical Sciences, University of Pittsburgh	2005 - present
- Member, University of Pittsburgh Cancer Institute	2005 - present
- Associate Director, Drug Discovery Institute, University of Pittsburgh	2005 - present
- Fellow, American Association for the Advancement of Science	2011 - present
- Editorial Advisory Board of Burger's Medicinal Chemistry and Drug Discovery	2008
- Editorial Advisory Board of Future Medicinal Chemistry	2009 - present
- Advisory Editorial Board for Medicinal Chemistry Communications	2009 - present

C. Contributions to Science

1. DDT Research: After doing a postdoctoral fellowship at the University of Toronto, I moved to the Eppley Institute for Research in Cancer at UNMC and collaborated with a pharmacologist interested in the mechanism responsible for the hepatocarcinogenicity of DDT in mice. I worked out the routes of metabolism of DDT in rodents that lead to the major metabolic products, including a reactive α-chloroepoxide metabolite. I did kinetic isotope experiments in animals, liver perfusion studies, mutation analysis using the Ames system, alkaline gradient analysis for DNA breaks, etc. as part of this effort that was funded by NCI for ~ 8 years. Eventually DDT was banned in the U.S.A. for environmental reasons so its carcinogenicity became a moot point, although its mechanism of action remains unknown.

Selected publications: Gold B, Leuschen T, Brunk G & Gingell, R. Metabolism of a DDT metabolite via a chloroepoxide. *Chem.-Biol. Interact.* **35**, 159-176 (1981); Gold B & Brunk B. Metabolism of 1,1,1-tri-chloro-2,2-bis(p-chlorophenyl)ethane and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane in the mouse. *Chem.Biol. Interact.* **41**, 327-339 (1982); Gold B & Brunk G. Metabolism of 1,1,1-trichloro-2,2-bis(p-chloro-phenyl)ethane (DDT), 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane and 1-chloro-2,2-bis(p-chloro-phenyl)ethene in the hamster. *Cancer Res.* **43**, 2644-2647 (1983); Gold B & Brunk G. A mechanistic study of the metabolism of 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane (DDD) to 2,2-bis(p-chlorophenyl)acetic acid (DDA). *Biochem. Pharmacol.* **33**, 979-982 (1984); Gold B & Brunk G. The effect of subchronic feeding of 1,1-di-chloro-2,2-bis(4'-chlorophenyl)ethene (DDE) on its metabolism in mice. *Carcinogenesis* **7**, 1149-1153 (1986).

2. Organ Specificity of N-nitroso compounds: It was assumed in the 1970' and 1980's that carcinogens in our food were responsible for human cancers and there was much effort to identify chemicals in our environment that were responsible. The formation of N-nitroso compounds from the reaction of amines, amides and ureas with nitrite found in saliva and added as a meat preservative became an area of intense research. Potential nitrosatable drugs and food additives also became a hot area of research. The N-nitroso compounds have the ability to induce cancers in virtually every organ (e.g., liver, esophagus, pancreas, colon, lung, kidney, brain, etc., based on their structure, route of administration dose and animal species. As part of this effort, I synthesized many N-nitroso compounds and determined their metabolism, reactions with nucleic acids and their carcinogenicity.

Selected publications: Althoff J, Grandjean C, Gold B & Runge R. Carcinogenicity of 1-oxopropyl-propylnitrosamine in Syrian golden hamsters. *Z. Krebsforsch.* **90**, 221-225 (1977); Gold B & Linder W. α-Hydroxynitrosamines: Transportable metabolites of dialkylnitrosamines. *J. Amer. Chem. Soc.* **101**, 6722-6723 (1979); Bulay O, Mirvish SS, Garcia H, Pelfrene AF & Gold B. Carcinogenicity tests of six nitrosamides and a nitrosocyanamide administered orally to rats. *J. Natl. Cancer Inst.* **62**, 1523-1528 (1979); Gold B & Brunk G. The effect of pyrazole, phenobarbital, ethanol and 3-methylcholanthrene pretreatment on the *in vivo* and *in vitro* genotoxicity of N-nitrosopyrrolidine. *Carcinogenesis* **9**, 1001-1006 (1988).

3. DNA Affinity Binding Alkylating Agents: As a result of research pioneered by the Dervan and Lown labs, it became possible to generate DNA damage in a sequence dependent manner by tethering alkylating agents

onto molecules that recognize specific sequences of DNA. We developed a number of molecules that were able to selectively alkylate DNA in the major vs. minor groove and with some sequence specificity. We demonstrated the sequence selectivity for simple methylating agents, e.g., MNU, MNNG, MMS. The most significant compound that we produced (Me-Lex) specifically generates N3-methyladenine, which we showed is a cytotoxic but not mutagenic lesion. The Me-Lex compound was used in a number of labs to selectively produce this lesion, which is an excellent substrate for alkyladenine-DNA glycosylase (AAG, MPG). This work was continuously supported by NIH from 1981-2012. Using the compounds we synthesized allowed us and others to probe the biology of specific DNA repair pathways.

Selected publications: Zhang Y, Chen F.X, Mehta P & Gold B. The design of groove and sequence selective alkylation of DNA by sulfonate esters tethered to lexitropsins. *Biochemistry* **32**, 7954-7965 (1993); Engelward BP, Weeda G, Wyatt MD, Broekhof JLM, de Wit J, Donker I, Allan JM, Gold B, Koeijmakers JHJ, & Samson LD. Base excision repair deficient mice lacking the Aag DNA glycosylase. *Proc. Natl. Acad. Sci.* **94**, 13087-13092 (1997); Kelly J, Inga A, Chen F.-X, Dande P, Shah D, Monti P, Aprile A, Burns PA, Scott G, Abbondandolo A, Gold B, & Fronza G. Relationship between DNA methylation and mutational patterns induced by a sequence selective minor groove methylating agents. *J. Biol. Chem.* **274**, 18327-18334 (1999); Shah S, Kelly J, Zhang Y, Dande P, Martinez J, Ortiz G, Fronza G, Tran H, Soto, MA, Marky L, & Gold, B. Evidence in *Escherichia coli* that N3-methyladenine lesions induced by a minor groove binding methyl sulfonate ester can be processed by both base and nucleotide excision repair. *Biochemistry* **40**, 1796-1803 (2001); Settles S, Wang R-W, Fronza G, & Gold, B. Effect of N3-Methyladenine and an isosteric stable analogue on DNA polymerization. *J. Nucleic Acids* **2010**, 426505 (2010); Fouquerel E, Svilar D, Sobol RW, Bobola MS, Silber, JR, & Gold B. Synthesis and characterization of DNA minor groove binding alkylating agents. *Chem. Res. Toxicol.* **26***,* 156–168 (2013).

4. Mechanism for Glycosylase Recognition of DNA Damage: We became interested in trying to inhibit DNA repair in order to enhance the activity of DNA damaging anticancer drugs. As part of this process, we began an extensive investigation of how different DNA adducts affected local DNA stability with the goal of relating instability to recognition by the initial DNA repair enzymes that must find their cognate lesions. This lead to multiple papers, including those in collaboration with Michael Stone (Vanderbilt) and Luis Marky (NYU and UNMC). This work was supported by NIH from 2001-2008.

Selected publications: Ganguly M, Wang R-W, Marky LA, & Gold B. Introduction of cationic charge into DNA near the major groove edge of a guanine•cytosine base pair: characterization of oligodeoxynucleotides substituted with 7-aminomethyl-7-deaza-2'-deoxyguanosine. *J. Am. Chem. Soc.* **131**, 12068-12069 (2009); (**b**) Singh SK, Szulik MW, Ganguly M, Khutsishvili I, Stone MP, Marky LA, & Gold B. Characterization of DNA with an 8-oxoguanine modification. *Nucleic Acids Res.* **39**, 6789-6801 (2011); (**c**) Ganguly M, Szulik MW, Donahue PS, Clancy K, Stone MP, & Gold B. Thermodynamic signature of DNA damage: characterization of DNA with a 5-hydroxy-2'-deoxy-cytidine•2'-deoxyguanosine base pair. *Biochemistry* **51**, 2018-2027 (2012); (**d**) Gold B, Stone MP, Marky LA. Looking for Waldo: A potential thermodynamic signature to DNA damage. *Acc. Chem. Res.* **47**, 1446-1454 (2014).

5. Design and Characterization of Inhibitors of AP Endonuclease-1/Redox Factor-1 (APE-1/Ref-1): As part of our effort to inhibit DNA repair, we have generated nM inhibitors of human APE-1. We have identified a synergism between our most potent inhibitor and a kinase inhibitor (Vemurafenib) used in the treatment of melanoma.

Selected Publications: Srinivasan A, Wang L, Cline CJ, Xie Z, Sobol RW, Xie X-Q, & Gold B. The identification and characterization of human AP endonuclease-1 inhibitors. *Biochemistry* **51**, 6246-6259 (2012); Srinivasan A, & Gold B. Small molecule inhibitors of DNA damage repair pathways: an approach to overcome tumor resistance to alkylating anticancer drugs. *Future Med. Chem.* **4**, 1093-1111 (2012); (**c**) Feng Z, Kochanek S, Close D, Wang LR, Srinivasan A, Almehizia AA, Iyer P, Xie Q-X, Johnston PA, & Gold B. (2015) Design and activity of AP endonuclease-1 inhibitors. *J. Chem. Biol.,* **8***.* 79-93.

A List of 108 Published Papers out of a total of 133 can be viewed at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/barry.gold.1/bibliography/41145416/public/?sort=date&direction=ascending

D. Research Support

On Going Research Support - none

Completed Research Support

P41 GM094055 (PI, Gold) 09/01/2010 - 05/01/2014; "Protein-protein interaction directed libraries." The goal of the grant is to produce 1,760 compounds based on 56 scaffolds aiming to (ant-) agonize protein-protein interaction.

P50-CA121973-07 (PI, Kirkwood) Sub-project on SPORE in Skin Cancer Developmental Research Program (co-I, B Gold) 08/01/2014 – 07/31/2015; "Identifying Synergy between APE1 DNA Repair Inhibitors and Approved Melanoma Cancer Drugs." The goal is to determine the synergistic relationship between inhibition of AP endoniuclease-1 and drugs, including B-Raf inhibitors, currently used to treat malignant melanoma