BIOGRAPHICAL SKETCH

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NAME: Daniel J. Canney

POSITION TITLE: Chair, Department of Pharmaceutical Sciences, Associate Professor of Medicinal Chemistry

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

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
Temple University, School of Pharmacy	B.S.	1979	Pharmacy
Temple University, School of Pharmacy	Ph.D.	1986	Medicinal Chemistry
Washington University, School of Medicine	Postdoc	1987-1990	Medicinal Chemistry

A. Personal Statement

My training in organic/medicinal chemistry, my experience carrying out structure-activity relationship structure studies on the proposed lactones (and related small molecules), my experience performing and/or evaluating data from *in vitro* and *in vivo* assays, and my leadership abilities make me highly qualified to successfully carry out the proposed research project with the support of my collaborators. I have a broad background in the application of medicinal chemistry approaches to structure-activity relationship studies involving novel ligands for pharmacologically important receptors. I have extensive experience in the design, synthesis and characterization of structurally diverse molecules of pharmacological interest that include serotonergic and muscarinic ligands, anticonvulsant agents, SPECT imaging agents, retinoic acid derivatives, and "drug" metabolites (resveratrol, Letrazole). In my laboratory or in collaboration with academic and industry scientists, these compounds have undergone a variety of biological assays in order to characterize *in vitro* and *in vivo* activity. At various times throughout my career (e.g., see anticonvulsant agents below) I was directly involved in the *in vivo* (ED_{50}, CD_{50}) and *in vitro* (IC_{50}, Ki) screening of compounds that I had designed and synthesized. The current proposal builds logically on our recent work that identified a series of lactone-based ligands as high affinity ligands (nanomolar affinity) for muscarinic and serotonin receptor subtypes. **We have shown that a subset of these lactone-based ligands exhibits high affinity and high selectivity for 5-HT_7 receptors and have promising drug-like properties.** These exciting, novel compounds will serve as leads in the current project. *Intellectual property surrounding these compounds have been covered in the patents/applications listed below*. My role is to use my considerable experience with this series of lactones and with related small molecules to direct the molecular modifications of our leads based on the results of the biological assays (structure-activity relationship studies; SAR studies). Hence I will oversee the design, synthesis, purification and characterization of newly designed ligands to improve pharmacokinetic and/or pharmacodynamic profiles based on the biological data collected. **The target compounds will be prepared using methods developed in my lab** or with well precedented literature methods. I will share the responsibilities of program leadership with Benjamin Blass ("Co-PI") including overall program direction, design, data interpretation, manuscript and patent preparation, and scientific presentations as appropriate. Selective 5-HT_7 receptor ligands represent a promising new strategy in the treatment of inflammatory bowel diseases that warrants further study.

a. Gao, R., Fan, R., **Canney, D.J.** Synthesis of β,β-disubstituted γ-butyrolactones by chemoselective oxidation of 1,4-diols and γ-hydroxy olefins with $RuCl_3/NaIO_4$, *Synlet*, **2015,** *26*(05): 661-66.
b. Gao, R., Bhandare, R., **Canney, D.J.** Homologation as a lead modification approach en route to a series of lactone-based muscarinic ligands, *Medicinal Chemistry Research*, **2014**, *23*:1023–1030.
c. Bhandare, R., **Canney, D.J.** Bioisosteric replacement in the design, synthesis and evaluation of ligands for muscarinic acetylcholine receptors, *Medicinal Chemistry Journal* (Bentham), **2014**, *10*(4):361-375.
d. **Canney, D. J.,** Lu, H-F., Holland, K. D., McKeon, A. C., Ferrendelli, J. A., and Covey, D.F. Synthesis and Evaluation of Fluorinated γ-Butyrolactones and γ-Thiobutyrolactones as Modulators of the GABA Receptor Complex. *Bioorg. Med. Chem.,* **1998***, 6,* 43-55.

Abstracts:

a. Blattner, K., **Canney, D.J.,** Gao, R., Gordon, J.C., Blass, B.E., Abou-Gharbia, M., Wang, H., Khan, W.I. Design and Synthesis of Selective 5-HT_7 Receptor Antagonists for the Treatment of Inflammatory Bowel Disease (IBD). *ACS National Meeting*, Boston, August, **2015**.

b. 5-HT7 Receptor Antagonists for the Treatment of Inflammatory Bowel Disease (IBD), Blass, B. E.; **Canney, D. J.;** Blattner, K.; Gao, R.; Gordon, KJ. C.; Abou-Gharbia, M.; Wang, H.; Khan, W. I. *BIO International Convention*, Philadelphia, PA, June **2015**.

- **Patents and patent applications**Novel Sigma-2 receptors binders and their method of use, **Canney, D.J**.; Gao, R.; Abou-Gharbia, M.; Blass, B. E., US Provisional 62 160, 355, **2015**.

- Preparation of dihydrofuran-2(3H)-one derivatives as 5-hydroxytryptamine receptor 7 activity modulators, **Canney, D. J.;** Gao, R.; Abou-Gharbia, M.; Blass, B. E. WO2014164756, **2014**.

- Novel Disubstituted oxazolidin-2-ones 5-HT2b activity modulators and their method of use, **Canney, D. J.;** Bhandare, Richie R.; Blass, B. E.; Abou-Gharbia, M., WO2014085413, **2014**.

- Novel 5-hydroxytryptamine receptor 7 activity modulators and their method of use, **Canney, D.J.;** Gao, R.; Abou-Gharbia, M.; Blass, B. E. US Provisional 61, 776,117, **2013**.

- Novel disubstituted oxazolidin-2-ones 5-HT2b activity modulators and their method of use, **Canney, D. J.;** Bhandare, Richie R.; Blass, B. E.; Abou-Gharbia, M., US Provisional 61,730,807, **2012**.

B. Positions and Honors

1987-1990 *Postdoctoral Fellow*, Department of Pharmacology and Molecular Biology, Washington University, School of Medicine, St. Louis, MO
1990-1993 *Research Assistant Professor,* Department of Radiology, Radiopharmaceutical Chemistry Section, University of Pennsylvania
1993-1998 *Assistant Professor of Medicinal Chemistry,* Department of Pharmaceutical Science, Temple University School of Pharmacy
1998-present *Associate Professor of Medicinal Chemistry,* Department of Pharmaceutical Science, Temple University School of Pharmacy
2002-present Director of Graduate Studies, Department of Pharmaceutical Sciences, Temple University School of Pharmacy
2011-present Chairperson, Department of Pharmaceutical Sciences, Temple University School of Pharmacy

Other Experience and Professional Memberships

2011-present Associate Editor, *Life Sciences*

2012-2015	N.I.H., SBIR grant reviewer
2011-present	AAAS Grant Reviewer; Research Competitiveness Program, (KACST)
2012-present	AAPS, Annual Meeting Poster reviewer
2013-present	AACP Grant Reviewer; New Investigator Award
2012	Temple University Outstanding Faculty Service Award
2008-2012	Graduate Board of Directors, Fellowship Committee
2002-2008	Graduate Board of Directors, Appeals Committee
2008-2009	American Association of Colleges of Pharmacy (AACP), Research and Graduate Affairs Committee
2001-present	Environmental Health and Safety (EHS) Committee
1994-present	Temple Univ., School of Pharmacy, Graduate Committee (Chair since 06/2002)
1995-2004	Director, Pharmaceutical Industry Post B.S. Training Program
1995-present	Member, American Association of Colleges of Pharmacy (AACP)
1981-present	Member, American Chemical Society (ACS)
1998-present	Member, American Pharmaceutical Association (APhA)
1998-present	Rho Chi Pharmaceutical Honor Society, Faculty Advisor and member
1998	Teacher of the Year Award, AACP

C. Contributions to Science

My postdoctoral training involved studies of novel neuroactive dihydro-2(3H)-furanone and thiophenone derivatives as potential anticonvulsants. These compounds acted as agonists, antagonists, or inverse agonists at the GABA receptor complex depending on the position and type of alkyl substituents on the lactone ring. Structure-activity relationship (SAR) studies ensued and the compounds were evaluated using standard anticonvulsant screening procedures in rodents (CD_{50}, ED_{50}), radioligand binding assays (IC_{50}) and electrophysiology experiments. Our work with these convulsant and anticonvulsant lactones furthered our understanding of allosteric modulators of the GABA receptor complex. In addition to synthesizing the compounds, I was directly involved in the *in vivo* evaluation of compounds **in mice** (ED_{50} and CD_{50} values) and in the radioligand binding assays (IC_{50}, Ki values). I also developed a GC method to determine brain concentrations of selected agents that enabled the correlation of *in vivo* and *in vitro* data with brain concentrations. Fluorinated lactones were also prepared to evaluate the effects of fluorination on the pharmacological properties to these compounds. Fluorine-NMR (^{19}F-NMR) chemical shift and relaxation (T_1 and T_2) data were used to characterize the interaction of the fluoro-derivatives with brain and other tissue preparations.

a. Holland, K. D., **Canney, D. J.,** Rothman, S. M., Ferrendelli, J. A., and Covey, D.F. Physiological Modulation of the GABA Receptor by Convulsant and Anticonvulsant Barbiturates in Cultured Rat Hippocampal Neurons. *Brain Research,* **1990,** *516*, 147-153.
b. Yoon, K-W., **Canney, D. J.,** Covey, D. F., and Rothman S.M. Modulation of Picrotoxin Receptors by Fluorinated Ethyl Methyl-γ-Butyrolactones. *J. Pharmacol. Exp. Ther.,* **1990,** *255*, 248-252.
c. **Canney, D. J.,** Holland, K. D., McKeon, A. C., Levine, J. A., Ferrendelli, J. A., and Covey, D. F. Synthesis and Structure-Activity Studies of Alkyl-Substituted γ-Butyrolactones and γ-Thiobutyrolactones: Ligands for the Picrotoxin Receptor. *J. Med. Chem.,* **1991,** *34*, 1460.
d. **Canney, D. J.,** Covey, D. F., and Evers, A. S. Direct Observation of a Fluorinated Anticonvulsant in Brain Tissue Using Using ^{19}F-NMR Techniques. *Biochem. Pharmacol.,* **1993**, *45*, *949-959.*

Several years of my training were spent in a Department of Radiopharmaceutical Chemistry. The development of potential imaging agents provided an opportunity to apply my synthetic and medicinal chemistry expertise to the design and synthesis of diamide-dimercaptide (N_2S_2)-Tc-99m complexes as organ-specific imaging agents and radioiodinated heterocyclic compounds as radioligands and/or brain-specific SPECT imaging agents. Compounds were evaluated in *in vitro* (radioligand binding and autoradiography) and *in vivo* in **rodents and primates**. This work led to the development of novel lead compounds as potential imaging agents for the kidney as well as for monoamine receptors in the CNS. I

served a leadership role in overseeing the progress of these projects as illustrated by first authorship on most of the manuscripts.

a. **Canney, D. J.,** Billings, J. I., Guo, Y-Z., Francesconi, L. C., Haggerty, B., S., Rheingold, A., L., and Kung, H. F. Dicarboxylate Diamide-Dimercaptide (N_2S_2) Technetium-99m Complexes: Synthesis and Biological Evaluation as Potential Renal Radiopharmaceuticals. *J. Med. Chem.,* **1993,** *36*, 1032- 1040.

b. **Canney, D. J.,** Guo, Y-Z., Kung, M.P., and Kung, H. F. Synthesis and Preliminary Evaluation of an Iodovinyl-Tetrabenazine Analog as a Marker for the Vesicular Monoamine Transporter. *J. Labeled Compds. and Radiopharm.,* **1993,** *33*, 355-368.

c. Kung, M.P., **Canney, D. J.,** Frederick, D., Zhuang, Z., Billings, J., and Kung, H. F. Binding of ^{125}1-Jodovinyltetrabenazine (^{125}1-TBZ) to CNS Vesicular Monoamine Transport Sites. *Synapse,* **1994,** *18*, 225-232.

d. **Canney, D. J.,** Kung, M.P., and Kung, H. F. Amino- and Amido-Tetrabenazine Derivatives: Synthesis and Evaluation as Potential Ligands for the Vesicular Monoamine Transporter. *Nucl. Med. Biol.,* **1995,** *22(4),* 527-535.

In an effort to develop subtype selective ligands for nicotinic receptors in the brain, a series of quinuclidine and related small molecules were designed, synthesized and evaluated through collaborations with industrial (Targacept) and academic (J. Buccafusco, Medical College of Georgia; M. Blanton, PhD, Texas Tech University) scientists. The results of those studies led to a novel series of quinucline-based ligands for the alpha4-beta-2 nicotinic subtype. I served a leadership role in overseeing the progress of these projects as illustrated in the first or last authorship of the manuscripts that came out of that work.

a. **Canney, D. J.,** Kemp, L., J., Zang, M., Gabriel, J., Webster, A., Buccafusco, J., Gattu, M., Doukas, P. H. Synthesis and preliminary biological evaluation of 3-substituted quinuclidines as nicotinic ligands. *Medicinal Chemistry Research,* **1997**, 7:5, 282-300.

b. **Canney, D. J.**, Buccafusco, J., Zhang, M., Doukas, P. H., Characterization of Ethyl (3-quinuclidinyl) acetate (EQA) as a Ligand for Cholinergic Receptors. *Life Sciences, Pharmacology Letters*, **1998**, *63:24*, PL 329-336.

c. Ahungena, A., Gabriel, J. L., **Canney, D. J.** Synthesis and Evaluation of 5-Substituted Derivatives of 4,5 Dihydro-3,3,-Diethyl-2-(3H)-Furanone as Subtype-Selective Muscarinic Leads. *Medicinal Chemistry Research,* **2003**, *12:9*, 481-511.

d. Sun, W., Blanton, M. P., Gabriel, J. L., **Canney, D. J.** Bioisosteric Replacement in the Design and Synthesis of Ligands for Nicotinic Acetylcholine Receptors. *Medicinal Chemistry Research***, 2005**, *14:5,* 241-259.

A molecular modeler (Dr. Jerome Gabriel) working with Dr. Dianne Soprano in the Department of Biochemistry at Temple University's, School of Medicine and I collaborated on a project focusing on the design and testing of retinoic acid receptor ligands. I went on to synthesize ligands that Dr. Gabriel designed in modeling experiments and found that several compounds had moderate affinity for the target receptor. Following molecular modifications on several scaffolds, high affinity ligands for RAR receptors were identified. My leadership role in these projects led to a series of novel ligands for retinoic acid receptors and the manuscripts (last author) below.

a. Nantogmah, S., Desai, S., Bhandare, R., Gabriel, J., Soprano, D., **Canney, D.J**. Synthesis and Preliminary Evaluation of Affinity for Retinoic Acid Receptors for Novel Organosilicon-Based retinoids. *Pharmaceutical Chemistry Journal*, **2012**, *45* (10), 612-621.

b. Sun, W., Carroll, P.J., Soprano, D., **Canney, D.J**. Identification of a Chromone-Based Retinoid Containing a Polyolefinic Side Chain via Facile Synthetic Routes. *Bioorg. Med Chem Lett.* **2009***,* 1*9:15,* 4339-42.

c. Desai, S., Sun, W., Gabriel, J. L., and **Canney, D. J.** The Synthesis and Preliminary Evaluation of Substituted Chromones, Coumarins, Chromanones, and Benzophenomones as Retinoic Acid Receptor Ligands. *Heterocyclic Communications***, 2008***, 14:3,* 129-137.

d. Sun, W., Desai, S., Piao, H., Carroll, P., and **Canney, D.J.** Wittig-Horner-Emmons Reactions of Triethyl-3-methyl-phosphonocrotonate with 3-Formylchromones en Route to Benzophenone-Based Retinoid Candidates. *Heterocycles*, **2007,** *71:3*, 557–567.

More recently, structure-activity relationship (SAR) studies involving ligands for GPCRs is an ongoing area of interest for my lab (also see references under Personal Statement above). Initial efforts directed at the development of subtype selective muscarinic ligands led to a series of lactone-based ligands that showed high affinity for muscarinic receptors but only modest selectivity. Further evaluation of the compounds in a broad screening assay uncovered a subset of these compounds that exhibit high affinity and high selectivity for 5-HT_7 receptors. Importantly, some of these compounds have also been shown to have drug-like properties. These promising, novel ligands are being used as lead compounds in the current project.

a. Bhandare, R., **Canney, D.J.** Bioisosteric replacement in the design, synthesis and evaluation of ligands for muscarinic acetylcholine receptors, *Medicinal Chemistry Journal* (Bentham), **2014**, 10(4):361-375.
b. Bhandare, R.R., **Canney, D.J**. Modifications to five-substituted 3,3-diethyl-4,5-dihydro-2(3H)-furanones *en* route to novel muscarinic receptor ligands. *Medicinal Chemistry Research,* **2010***, 20* (5), 558-565*.*
c. Gao, R., **Canney, D.J.** A Versatile and Practical Microwave Assisted Synthesis of Sterically Hindered N-Aryl Piperazines, *J. Org. Chem.*, **2010**, *75* (21), 7451–7453.
d. Gao, R., **Canney, D.J.** A modified Prins reaction for the facile synthesis of structurally diverse substituted 5-(2-hydroxyethyl)-3,3-dihydrofurane-2(3H)-ones. *Tetrahedron Lett.*, **2009**, *50;43*, 5914-5916.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1Tqau-nKws9Qw/bibliography/48085335/public/?sort=date&direction=ascending

D. Research Support

During my earlier years at Temple University, modest funding to support my laboratory was obtained primarily through internal grants and funds from the pharmaceutical industry. With the state-of-the-art equipment, instrumentation, laboratory space, and talented scientists now available in the Moulder Center for Drug Discovery Research my efforts to attract external funding have intensified.

- STTR Grant # 1 R41 AG052249-01. Novel Sigma-2 receptor antagonists for the treatment of Alzheimer's Disease. 10% effort, Co-I, National Institute of Health, $298,500.00, budget period 09/01/2015 - 08-30-2016.

- Grant # 1R03CA133943-01A1, Conjugation of anticancer drugs, Swati Nagar,, PhD, PI, Daniel Canney, PhD, Co-investigator, National Cancer Institute, $150,000, 10 % effort, budget period 06/01/2009 - 05/31/2011.

- Grant-in-Aid of Research. Project title: Evaluation of Newly Designed Muscarinic Ligands in Radioligand Binding Assays. Funds obtained through the University were used to evaluate test compounds in binding assays at CEREP. Budget period 01/01/09 – 12/31/09, $ 3,000.00

- *Industry-sponsored Training Program in Medicinal Chemistry*, Zeneca Pharmaceuticals sponsored a program whereby an M.S. graduate student was supported as an RA while obtaining practical laboratory experience in medicinal chemistry at Temple University, School of Pharmacy. Budget Period, 8/2002-8/2004, $25,000.00,

- *New, Previously Unfunded Directions for Established Investigators Grant Program (Office of*

Vice-Provost for Research), Design, synthesis, and evaluation of subtype-selective ligands for retinoic acid receptors, Budget Period, 01/2003-01/2005, $48,000.