

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
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NAME Charles E. McKenna		POSITION TITLE Professor of Chemistry and Pharmacology & Pharmaceutical Sciences	
eRA COMMONS USER NAME (credential, e.g., agency login) CEMCKENNA			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Oakland University	B.A.	05/66	French Literature
University of California, San Diego	Ph.D.	08/71	Chemistry
University of California, San Diego	Postdoctoral	08/71	Biochemistry
Harvard University	Postdoctoral	08/73	Bio-Organic Chemistry

**A. Personal Statement**

The goal of this Supplemental project is to synthesize nucleotide analogs designed to selectively and potently inhibit DNA Pol  $\beta$  and modify them to achieve effective inhibitors of cancer cells. My primary field of research is medicinal chemistry, bio-organic phosphorus chemistry, with a particular interest in the synthesis, function and therapeutic potential of nucleotide analogues. I have long experience in the field of bio-active phosphonates, including design and synthesis of phosphonate prodrug scaffolds. I believe that I am well qualified to lead this research project on the basis of extensive prior experience in similar research collaborations involving chemists, biologists, and pharmacologists. I also have practical experience in translation (see "Other Experience" below) and am a named inventor on more than 10 drug-related patents. At USC, I founded the Interdisciplinary Program in Drug Discovery (iPIDD) of Dornsife College Chemistry and the School of Pharmacy.

**B. Positions and Honors****Positions and Employment**

1971-1972	Research Associate, UC, San Diego (with T.G. Traylor and M.D. Kamen)
1972-1973	Research Fellow, Harvard University (with F.H. Westheimer)
1973	Visiting Scientist, A.N. Bakh Academy of Sciences Institute of Biochemistry
1973-1979	Assistant Professor of Chemistry, University of Southern California
1980-1988	Associate Professor of Chemistry, University of Southern California
1989-present	Professor of Chemistry, University of Southern California
2000-2006	Professor of Pharmaceutical Sciences, University of Southern California
2006-present	Professor of Pharmacology and Pharmaceutical Sciences, University of Southern California
2006-2008	Head, Inorganic/Bio Division, Department of Chemistry, University of Southern California
2008-2011	Chair, Department of Chemistry, University of Southern California
2012-	Vice Dean for Natural Sciences, USC Dornsife College of Letters, Arts & Sciences

**Other Experience and Professional Memberships**

1979	Co-organizer, US-Japan Symposium on Bio-organic Chemistry, ACS-CSJ Chemical Congress
1979-1982	Organic Division representative, Inter-divisional Symposium Planning Committee, ACS
1986-present	ACS-Frasch Foundation Grant Awards Committee (1986-2011)
1991	External Reviewer, Killam Fellowship
1991, 1995	NIH Special Study Section (AIDS)
1991-present	USC Institute for Genetic Medicine
1993-2000	NIH Study Section Z (1993, 1994, 1997, 1998, 2000)
1994-present	Consultant, Oridigm Corp. (1994); Per Ardua Corp. (1996); Neurochem, Inc. (1998); Polygon Southwest, Inc. (1999); Geltex Pharmaceuticals, Inc. (2000); Western Systems Specialists, Inc.

(2000); Procter & Gamble Pharmaceuticals, Inc. (2003-2008)  
 1995-present International Scientific Board, International Conf. on Phosphorus Chemistry (ICPC)  
 1996-1998 Co-Program Organizer, ICPC14  
 1996-2002 Editor, ICPC14 Website (<http://www.usc.edu/dept/chemistry/ICPC14/>)  
 1998-2002 Scientific Director, BioKeys Pharmaceuticals, Inc.  
 2001 International Scientific Board, Post-ICPC XV Symposium in Life Sciences  
 2002-2004 Program Chair, ICPC16  
 2003-present Editorial Advisory Board, *Molecular Pharmaceutics*  
 2004-present Director, Interdisciplinary Program in Drug Discovery at USC (iPIDD)  
 2007 NIH-NIAID SRG (AIDS Therapeutics Development)  
 2007 NSF SBIR/STTR Review Panel, Drug Delivery  
 2007-present International Scientific Board, ICCPC  
 Member: American Society of Biochemists and Molecular Biologists, American Chemical Society, International Society for Antiviral Research, AAAS

### Honors

1972-1973 National Institutes of Health Postdoctoral Fellowship  
 1973 National Academy of Sciences Exchange Scholar  
 1980 Osaka University Fellowship (declined)  
 1998 Provost commendation for "extraordinary performance" in GE Program  
 2003 CET Faculty Fellow; Distinguished Fellow, 2006-  
 2003 College GE Teaching Award  
 2004 USC Ambassadors  
 2005 Distinguished Alumni Achievement Award, Oakland University  
 2005 Chemistry Department Alumni Award, Oakland University  
 2005 Elected Fellow, American Association for the Advancement of Science  
 2006 USC Associates Award for Excellence in Teaching  
 2006 Nanqiang Lecturer, Xiamen University  
 2006 Plenary Lecturer, National Conference on Phosphorus Chemistry, Zhengzhou, China  
 2007 Keynote Lecturer, 17<sup>th</sup> International Conference on Phosphorus Chemistry, Xiamen, China  
 2007-present Co-Director, Executive Committee, International Scientific Board, ICPC  
 2007 Phi Kappa Phi Faculty Recognition Award  
 2008 Keynote Lecturer, 15<sup>th</sup> International Conference Phosphorus Compounds, St. Petersburg  
 2008 Special Lecturer, 5th Key-Bridge Chemistry, Biology & Materials Conference, Tainan, Taiwan  
 2009 Raubenheimer Award  
 2009 USC General Education Distinguished Service Teaching Award  
 2010 Program Committee, International Conference on Antiviral Research  
 2010 USC Provost's Prize for Teaching with Technology  
 2011 Mellon Mentoring Award  
 2012 Plenary Lecturer, Saxon Biotech Symposium, Leipzig  
 2012 Plenary Lecturer, 19th International Conference on Phosphorus Chemistry, Rotterdam  
 2012 Chevalier des Palmes Académiques

### C. Selected Peer-reviewed Publications (Selected from > 180 publications)

#### Most Relevant to the Current Application

1. Wu Y, Zakharova VM, Kashemirov BA, Goodman MF, Batra VK, Wilson SH, McKenna CE.  $\beta,\gamma$ -CHF- and  $\beta,\gamma$ -CHCl-dGTP Diastereomers: Synthesis, Discrete 31P NMR Signatures, and Absolute Configurations of New Stereochemical Probes for DNA Polymerases. *J Am Chem Soc.* 2012;134(21):8734-8737.
2. Chamberlain BT, Batra VK, Beard WA, Kadina AP, Shock DD, Kashemirov BA, McKenna CE. Stereospecific Formation of a Ternary Complex of (S)- $\alpha,\beta$ -fluoromethylene-dATP with DNA Pol  $\beta$ . *ChemBioChem.* 2012;13(4):528-530. PMID: 22315190.
3. Chamberlain BT, Upton TG, Kashemirov BA, McKenna CE.  $\alpha$ -Azido bisphosphonates: synthesis and nucleotide analogues. *J Org Chem.* 2011;76:5132-5136. PMID: 21462930.
4. Eriksson U, Peterson LW, Kashemirov BA, Hilfinger JM, Drach JC, Borysko KZ, Breitenbach JM, Kim JS,

Mitchell S, Kijek P, McKenna CE. Serine peptide phosphoester prodrugs of cyclic cidofovir: Synthesis, transport, and antiviral activity. *Mol Pharm*. 2008; 5(4):598-609. PubMed PMID: 18481868; PubMed Central PMCID: PMC2629803.

5. McKenna CE, Kashemirov BA, Peterson LW, Goodman MF. Modifications to the dNTP triphosphate moiety: from mechanistic probes for DNA polymerases to antiviral and anti-cancer drug design. *Biochim Biophys Acta* 2010 1804: 1223-1230. PubMed PMID: 20079885.

### Ten Additional Recent Publications

1. Batra VK, Shock DD, Beard WA, McKenna CE, Wilson SH. Crystal structure of DNA polymerase  $\beta$  reveals conformational equilibrium of the 8-oxo-7,8-dihydrodeoxyguanosine lesion in the template base position. *Proc Nat Acad Sci U S A*. 2012;109(1):113-118. PMCID: PMC3252918.
2. Peterson LW, Kim JW, Kijek P, Mitchell S, Hilfinger JM, Breitenbach JM, Borysko KZ, Drach JC, Kashemirov BA, McKenna CE. Synthesis, transport and antiviral activity of Ala-Ser and Val-Ser prodrugs of cidofovir. *Bioorg Med Chem Lett*. 2011; 21:4045-4049. PubMed PMID: 21641218; PubMed Central PMCID: PMC3115518.
3. Ebetino FH, Hogan AM, Sun S, Tsoumpra MK, Duan X, Triffitt JT, Kwaasi AA, Dunford JE, Barnett BL, Oppermann U, Lundy MW, Boyde A, Kashemirov BA, McKenna CE, Russell RG. The relationship between the chemistry and biological activity of the bisphosphonates. *Bone*. 2011; 49:20-33. PMID: 21497677.
4. Tian X, Jin RU, Bredemeyer AJ, Oates EJ, Blazewska KM, McKenna CE, Mills JC. Rab26 and rab3d are direct transcriptional targets of mist1 that regulate exocrine granule maturation. *Mol Cell Biol*. 2010; 30(5):1269-1284. PubMed PMID: 20038531; PubMed Central PMCID: PMC2820885.
5. Batra VK, Pedersen LC, Beard WA, Wilson SH, Kashemirov BA, Upton TG, Goodman MF, McKenna CE. Halogenated  $\beta,\gamma$ -methylene- and ethylidene-dGTP-DNA ternary complexes with DNA polymerase  $\beta$ : Structural evidence for stereospecific binding of the fluoromethylene analogues. *J Am Chem Soc*. 2010; 132(22):7617-7625. PubMed PMID: 20465217; PubMed Central PMCID: PMC2891752.
6. McKenna CE, Kashemirov BA, Blazewska KM, Mallard-Favier I, Stewart CA, Rojas J, Lundy MW, Ebetino FH, Baron RA, Dunford JE, Kirsten ML, Seabra MC, Bala JL, Marma MS, Rogers MJ, Coxon FP. Synthesis, chiral high performance liquid chromatographic resolution and enantiospecific activity of a potent new geranylgeranyl transferase inhibitor, 2-hydroxy-3-imidazo[1,2-a]pyridin-3-yl-2-phosphonopropionic acid. *J Med Chem*. 2010; 53(9):3454-3464. PubMed PMID: 20394422.
7. Upton TG, Kashemirov BA, McKenna CE, Goodman MF, Prakash GK, Kultyshev R, et al. A, $\beta$ -difluoromethylene deoxynucleoside 5'-triphosphates: A convenient synthesis of useful probes for DNA polymerase  $\beta$  structure and function. *Org Lett*. 2009; 11(9):1883-1886. PubMed PMID: 19351147; PubMed Central PMCID: PMC2722935.
8. Eriksson U, Hilfinger JM, Kim JS, Mitchell S, Kijek P, Borysko KZ, Breitenbach JM, Drach JC, Kashemirov BA, McKenna CE. Synthesis and biological activation of an ethylene glycol-linked amino acid conjugate of cyclic cidofovir. *Bioorg Med Chem Lett*. 2007; 17(3):583-586. PubMed PMID: 17161946; PubMed Central PMCID: PMC1899532.
9. Baron RA, Tavaré R, Figueiredo AC, Blazewska KM, Kashemirov BA, McKenna CE, Ebetino FH, Taylor A, Rogers MJ, Coxon FP, Seabra MC. Phosphonocarboxylates inhibit the second geranylgeranyl addition by rab geranylgeranyl transferase. *J Biol Chem*. 2009; 284(11):6861-6868. PubMed PMID: 19074143; PubMed Central PMCID: PMC2652301.
10. Williams MM, Krylov IS, Zakharova VM, Serpi M, Peterson LW, Krečmerová M, Kashemirov BA, McKenna CE. Cyclic and acyclic phosphonate tyrosine ester prodrugs of acyclic nucleoside phosphonates. *Coll Symp Ser*. 2011; 12:167-170.

### D. Research Support

#### Ongoing Research Support

USC-LAS College	McKenna, C.E. (PI)	08/01/2008 - 07/31/2012
"Unrestricted Research Account"		Role: PI

Research account provided by the USC College of Letters, Arts, and Sciences.

AMVIS	McKenna, C.E.; Krečmerová, M. (co-PI)	01/01/2010 - 12/31/2012
"Preparation of Peptidomimetic Prodrugs of Acyclic Nucleoside Phosphonates as Antivirals with Improved		

Bioavailability” Role: Co-PI  
 U.S. and Czech research cooperation grant, provides partial travel support only to develop a collaboration.

NIH: U19CA105010 Goodman, M. (PI) 08/16/2004 - 07/31/2013  
 “DNA Polymerase Fidelity Mechanisms. Theory and Experiment” Role: Senior Investigator  
 The goal is to provide synthetic and modeling support for a collaborative effort to apply dNTP analogues as probes of DNA polymerase beta.

FACE: Partner University Fund McKenna, C.E. (PI) 04/01/2010 - 03/31/2013  
 “Joint Research at the Chemistry-Biology Interface” Role: PI  
 The goal of this project is to design and create novel inhibitors of Brdt, a testis-specific member of the BET protein family, in collaboration with the Institut de Biologie Structurale (IBS) and the Institut Albert Bonniot (IAB) in Grenoble, France.

NIH: R01 DC009837 McKenna, M.J. (PI) 03/01/2010 - 02/28/2015  
 “Drug-eluting Stapes Prosthesis” Role: USC PI  
 The goal of this project in collaboration with MEEI-Harvard Medical School is to use fluorescent bisphosphonates to develop a drug delivery method to treat otosclerosis.

NSF: CRIF McKenna, C.E. (PI) 03/01/2011-28/02/2014  
 “Acquisition of an X-ray diffractometer at USC” Role: PI  
 Instrumentation grant.

**Completed Research Support**

NIH: R43AI091216 Hilfinger, J.M. (PI) 07/01/2010 - 06/30/2012  
 “Novel Prodrugs for Treatment of Human CMV Infections” Role: USC PI  
 Study peptidomimetic P-O esters of cidofovir for evaluation against cytomegalovirus.

Warner Chilcott Pharmaceuticals McKenna, C.E. (PI) 03/01/2003 - 03/30/2012  
 “Bisphosphonate Analog Synthesis” Role: PI  
 The goal of this project is to clarify mechanisms of action of bone-active drugs using new imaging tools under development in our laboratory.

NIH: S10RR028992 Qin, P. (PI) 12/01/2009 - 11/30/2011  
 “Acquisition of a Pulse EPR Spectrometer” Role: Major Participant  
 Instrumentation grant.

NIH: R44AI056864 Hilfinger, J.M. (PI) 08/15/2007 - 06/30/2011  
 “Improving Absorption and Targeting of Antiviral Drugs” Role: USC PI  
 The objective was to acquire and evaluate SAR of certain cyclic cidofovir prodrugs targeting smallpox.

NSF: 0821671 Roberts, R. (PI) 08/01/2008 - 07/31/2011  
 “Acquisition of a 600 MHz NMR at the University of Southern California” Role: Participant  
 Instrumentation grant.

NIH: U01 AI061457 Hilfinger, J.M. (PI) 02/01/2005 - 01/31/2010  
 “Oral Antiviral Prodrugs for Biodefense Initiative” Role: PI, USC  
 The objective was to synthesize and evaluate the SAR and pharmacokinetics of new serine peptide prodrugs of foscarnet and acyclic nucleotide analogues.

P&G Pharmaceuticals McKenna, C.E. (PI) 11/18/2003 - 05/31/2010  
 “Bisphosphonate Optimization” Role: PI  
 The goal of this project was to obtain more potent bisphosphonate drugs for osteoporosis and cancer.