CURRICULUM VITAE

A. BIOGRAPHICAL INFORMATION

Xiang-Qun (Sean) Xie, MD, PhD, EMBA 解向群

Associate Dean for Research Innovation School of Pharmacy
Professor of Pharmaceutical Sciences/Drug Discovery Institute,
Director of NIH Center of Excellence for Computational Drug Abuse Research
Director of Computational Chemical Genomics Research Center
Dept. of Pharmaceutical Sciences/Drug Discovery Institute
School of Pharmacy, University of Pittsburgh,
335 Sutherland Drive, 206 Salk Pavilion,
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School website: http://www.pharmacy.pitt.edu/Directory/profile.php?profile=425&type=Faculty
Xie websites: www.CBLigand.org/xielab www.CBLigand.org/CCGS www.CDARcenter.org

CAREER HIGHLIGHTS (Sean Xie)

23 years of teaching, research, administrative and scholarly service in 3 US Colleges of Pharmacy.

LEADERSHIP AND ADMINISTRATION EXPERIENCE

- **Executive MBA**. Formal education and training in managerial communications, leadership, and interpersonal dynamics, as well as knowledge of strategic planning and research administration.
- **Leadership Training Certificate.** The Shared Leadership Cohort Development Experience Workshop Training by JPorcari & Associates, LLC.
- **Extensive Management Experience**
  - ***Associate Dean for Research Innovation*****,** School of Pharmacy, University of Pittsburgh (UPitt)
    - ***Founding Director*** *of* Computational Chemical Genomics Screening Center, School of Pharmacy, UPitt.
    - ***Director/PI*** of NIH-funded Center of Excellence for Computational Chemogenomics Drug Abuse Research under joint Pitt and CMU consortium (P30DA035778, $5.6 million, 2014-2019)
    - ***Program Director,*** developed Pharmacometrics System Pharmacology (PSP) MS graduate program at School of Pharmacy University of Pittsburgh
  - ***Founding Director*** of the Pharmacoinformatics Research Center (PIRC), College of Pharmacy, University of Houston; ***Director/PI*** led a NIH P20 Cheminformatics research center grant (P20 HG003892, not funded) by six institutions (UH, Rice, MD Anderson, Baylor, UTHSC and UTMB).
  - ***Director*** of the IMS NMR facility center, University of Connecticut
  - ***Chair*** of the Graduate Admission Committee, School of Pharmacy; ***Chair*** of the Distinguished Lecture Series Committee, School of Pharmacy, University of Pittsburgh.
  - **A Member** of Leadership and Steering Committee, and ***Member*** of Planning and Budgeting Committee, School of Pharmacy, University of Pittsburgh.
- Entrepreneurship in translational R&D
  - **Founder/CSO and Chairman of the Board** of ID4Pharma LLC and Innovation Discovery Lab LLC, a University of Pittsburgh spinoff start companies, Pittsburgh PA,
  - **Entrepreneurship** in translational research and development and also successfully received federal SBIR Fast track grant for FDA IND-enabling anti-tumor drug R&D studies.

RESEARCH AND EDUCATION EXPERIENCE

- **PI of NIH funded Center Grant and R01 projects** (active: NIH P30DA035778 as Director/PI; DOD W81XWH-16-1-0490 as PI. Completed as PI: R01DA025612R01DA015770 R01DA015417, HL109654 and R29DA011510); **PI** of three industrial projects.
- **Co-PI/Core co-Director** of two NIH funded center grants (P50 GM06082, U54 MH074411) and one NIH funded Pharmacoinformatics training grant (T90 DK070109)
- **Industry partnership and consultant** for pharma & biotech, including Pfizer, Boston Scientific, Intel.
- **Extensive teaching** experiences in Pharm D and graduate education and training.
- **Co-PI/Training Mentor** of NIH and NSF Training Grants:
  - NIH T90 DK070109 Pharmacoinformatics training grant
  - CMU/PITT Joint Computational Biology PhD program
  - Swanson School of Engineering Undergraduate Summer Research Program
  - NSF Fellowship Computational Biology Undergraduate Research Program

RECENT NATIONAL AND INTERNATIONAL SCHOLARLY SERVICES AND COMMITTEES

- ***Charter Member of Science Board to*** *the Food and Drug Administration Advisory Committee (2014-2018)*
- ***Charter Member*** *of NIH Biophysics of Neural Systems (BPNS) Study Section (2010-2015),* ***Ad hoc member*** of NIH Biomedical Library and Informatics Review Committee (BLIRC), NIH Macromolecular Structure and Function D Study section (MSFD); ***Invited Special Emphasis Panelist*** for NIH NIDA ZDA1 MXL-F.
- ***Invited*** NIH MLSCN Steering Committee Meeting; NIH Roadmap Committee Meeting: Defining the Role of Informatics within the Molecular Libraries Program (MLP);
- ***Invited Expert Panel Reviewer*** for the Natural Science Foundation China (NSFC); ***Invited International Assessment Panelist*** for Fudan University College of Pharmacy; Honorable Professor of Chinese Academy of Medical Sciences & Peking Union Medical College, Fudan University.
- ***Invited Expert Reviewer*** of Molecular and Cellular Medicine Board (MCMB) for Medical Research Council (***MRC***) Foundation, United Kingdom; **Invited grant reviewer** for Netherlands Organization for Scientific Research (NWO), Council for Chemical Sciences (CW); **Invited Reviewer** for The Wellcome Trust Fund, Sir Henry Wellcome Fellowship, London, UK and the Austrian Science Fund.
- ***Editorial Board Member*** *of American Association of Pharmaceutical Scientists (AAPS) Journal,* ***Associate Editor*** of *BMC Pharmacol & Tox J and J.* of *American Journal of Molecular Biology.*
- ***Keynote Speaker and Organizing Committee*** *of 2015 AAPS Annual meeting "Symposium of Pharmaceutical Sciences in the Era of Big Data"; and 2013 MedChem & CADD.* ***Chair*** of 2008 International Drug Discovery and Technology Symposium: "In silico and in vitro chemical genomics screenings for GPCR Drug Discovery" Beijing; **Leading organizer/Chair** of 2006 American Society (ACS) Southwest Regional Meeting - NMR Symposium, Houston, Texas. ***Session chair*** of International Medicinal Chemistry Symposium, Beijing.

RECENT AWARD:

- *2014* ***AAPS*** Outstanding Research Achievement Award;
- 2017 ***Sino-American Pharmaceutical Professional Association (SAPA)*** Roadshow Competition (Final Award);
- 2017 ***Joint US Silicon Valley-China JiaShan Global Innovation Competition*** *(****Final Award****)*
- 2017 Nomination of ***Chancellor's Outstanding Research Award***

EDUCATION AND TRAINING

Executive MBA	School of Business Administration, University of Connecticut, Storrs, Connecticut Executive MBA (Executive Master of Business Administration)	2001-2003
Post-Doc.	MIT Francis Bitter National Magnet laboratory, Cambridge, MA /University of Connecticut Biophysics	1993-1995
Ph.D.	School of Pharmacy, University of Connecticut, Storrs, Connecticut Pharmaceutical Sciences (Medicinal Chemistry) (Ad: Alexadros Makriyannis). Graduated with the ***Summa cum laude*** *honor* Award for his academic excellence An elected Member of The Honor Society of ***PHI KAPPA PHI***	1989-1993
M.S.	Department of Chemistry, University of Connecticut, Storrs, Connecticut	1987-1988
M.D.	College of Pharmacy, Second Military Medical University, Shanghai, China	1978-1982

PROFESSIONAL EXPERIENCE

Current Faculty Positions at University of Pittsburgh (UP)

2014-pres.	**Associate Dean** for Research Innovation, School of Pharmacy, University of Pittsburgh
2006/8 - present	**Tenured Full Professor** of Pharmaceutical Sciences/Drug Discovery Institute, School of Pharmacy, University of Pittsburgh
2011/9- present	**Founding Director** of Computational Chemical Genomics Screening Center, School of Pharmacy, University of Pittsburgh
2014- present	**Director/PI** of NIH NIDA National Center of Excellence for Computational Chemogenomics Drug Abuse Research (CDAR) by organizing a collective cross-campus and cross-institution initiative at Pittsburgh area. www.CDARcenter.org
2014-pres.	**Founder/CSO and Chairman of the Board** of ID4Pharma LLC, the University of Pittsburgh spinoff start companies in Pittsburgh PA. Entrepreneurship in translational research and development and also successfully received federal SBIR Fast track grant for FDA IND-enabling anti-tumor drug R&D.
2018-pres.	**Founder** of the University of Pittsburgh spinoff startup company, Innovation Discovery Lab LLC, Pittsburgh PA for translational cannabinoid small-molecule drug R&D
2010 - present	**A Member** of Planning and Budgeting Committee, School of Pharmacy, University of Pittsburgh
2011 - present	**A Member** of Leadership and Steering Committee, School of Pharmacy, University of Pittsburgh
2008- present	**A member** of Graduate Program Council, School of Pharmacy. Chair of Graduate Admission for MediChem Track, School of Pharmacy, University of Pittsburgh.
2015/8-present	**Self-Study Group** - **Resources"** for the ACPE Accreditation Self-Study for the University of Pittsburgh School of Pharmacy for upcoming ACPE Accreditation Site Visit October 18-20, 2016

2008-2010 **Chair** of Graduate Student **Admission**, School of Pharmacy, U Pittsburgh

2008/10 -2008/9 **Co-PI/Core Co-Director** of Pittsburgh Center for Chemical Methodologies & Library Development (UPCMLD), University of Pittsburgh

2011/9-2013/8 **Co-PI/Core Director** of University of Pittsburgh Center for Diversity Chemistry (UP-CDC), University of Pittsburgh

2006/8 -2009/7 **Faculty and Co-PI** of the NIH roadmap funded Pittsburgh Molecular Library Screening Center (PMLSC) and Pittsburgh Drug Discovery Institute, University of Pittsburgh

2006/8 - present **Joint Faculty** of Carnegie Mellon University and Universit of Pittsburgn (CMU-Pitt) Ph.D. Computational Biology Program, Department of Computational-System Biology and Dept of Molecular Biophysics & Structural Biology (MBSB), School of Medicine, University of Pittsburgh

2008/5-present **Faculty member** of the Molecular Therapeutics and Drug Discovery/Development program, Pittsburgh Cancer Institute, U. of Pittsburgh

Previous Faculty Positions at Other Institutions

2003/12-2006/7 **Tenured Associate/Full Professor** of the Medicinal Chemistry, Dept of Pharmacological & Pharmaceutical Science, College of Pharmacy, University of Houston (UH), Houston, Texas

2005/10-2006/7 **Founding Director** of Pharmacoinformatics Research Center (PIRC), College of Pharmacy, University of Houston.

2005/8-2006/7 **Joint Faculty**, Dept of Biochemistry & Biology, UH, Houston, Texas

2005/3- 2006/8 **Executive Committee Member and Participating Faculty Member/Mentor** of the NIH Pharmacoinformatics Training Program (PI: George Stancel), University of Texas Health Science Center (UT-HSC), Houston Gulf Coast Consortia(GCC)

2005/3- 2006/8 **Director of Chemistry Coordinating Center** – Chemistry Unit of the new GCC initiative – Chemical Genomics Screening Center(CGSC) Houston (managing and coordinating the medicinal chemistry and computational chemistry projects among six GCC institutes: Baylor, MD Anderson, Rice, UH, UTHS, UTMB) (PI: Peter Davies).

2005/5- 2006/8 **Participating Faculty Member/Mentor** of the NIH Nanobiology Training Program, University of Texas Health Science Center (UT-HSC), Houston, Gulf Coast Consortia(GCC) (PI: M. Pettit)

2004/11- 2006/8 **Participating Faculty Member** of Keck Center for Computational & Structural Biology, Rice University, Houston, Gulf Coast Consortia, Texas

2004/4- present **Participating Faculty Member** of Institute of Molecular Design at the UH

1995/6-2003/11 **Director o**f IMS NMR Laboratory, Assistant/Associate Research Professor of Biomedical Science, Institute of Materials Science, University of Connecticut, Storrs, Connecticut

1995/5-2003/11 **Adjunct Assistant and Associate Professors**, Dept. of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut, Storrs, Connecticut.

06/93-04/95 **Post-Doctoral Fellow**, MIT Francis Bitter National Magnet laboratory, Cambridge, MA, / University of Connecticut Biophysics.

1982/9-1987/1 **Research Fellow/Lecturer**, Dept of Pharmaceutical Analysis. College of Pharmacy, Second Military Medical University, Shanghai, China

2001 - 2005 **Guest Professor**, College of Pharmacy, Zhejiang University, HongZhou, China

2010 - 2013 **Guest Scientist,** Stem Cell Medical Center, Chinese Academy of Medical Sciences, Tianjin Institute of Hematology & Blood Diseases Hospital

2010 - **Guest Professor,** College of Pharmacy, Fudan University, Shanghai, China

2011 - **Guest Professor,** College of Pharmacy, Jiaotong University, Shanghai, China

2013 - **XieHe Scholar Honorary Professor**, Chinese Academy of Medical Sciences & Peking Union Medical College

PROFESSIONAL, COMMITTEE SERVICES, AND GRANT REVIEW PANEL

2015/1-pres. **Charter Member of FDA Science Board Committee**, the United States Food and Drug Administration

2016/1-Present **Editorial Advisory Board Member** of American Association of Pharmaceutical Scientists (AAPS) Journal

2016/6 **Session Chair and invited speaker**, 2016, International Drug Discovery Science and Technology (IDDST), GoYang, Seoul, South Korea

2016/5 **Review Panelist** of the Graduate Program Review Site Visit for College of Pharmacy, Fudan University, Shanghai China, May 27, 2016

2016/6 **Session Chair and invited speaker**, 2016, International Drug Discovery Science and Technology (IDDST), GoYang, Seoul, South Korea

2015/8 ***Ad Hoc* Expert Reviewer** of the Austrian Science Fund (FWF, *Fonds zur Förderung der wissenschaftlichen Forschung*) Erwin Schrödinger Fellowship

2015/5 **Review Team** of Graduate Program Review Site Visit for Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston Texas

2015/3 **NIH Site Visit Panelist** of P41 Program Project (ZRG1 BCMBS 40) for National Resource for Dynamic Protein NMR Structures and Complexes NIH Site Visit Review

2015/1 – 2016/1 **Member of the Scientific Advisory Board**, Oxis Biotech company

2013/10 **Invited Keynote Speaker and Session Chair**, 2013, 144th OMICS Group Conference, 2nd International Conference on Medicinal Chemistry & Computer Aided Drug Designing (MedChem & CADD-2013), Las Vegas, USA

2013/7 **Invited Oversea Expert Panel Reviewer** for Chinese Natural Sciences Foundation

2015/7	(CNSF) Key Grant Review Panel Meeting for Pharmaceutical Sciences Key Program, Beijing, China
2013/3	**IAR Reviewer Invitation** for ZRG1 BST-J (40) P - PAR-11-220 NIGMS Program Project Review - Special Emphasis Panel/Scientific Review Group.
2012/12	**Invited grant reviewer** for Netherlands Organization for Scientific Research (NWO), Council for Chemical Sciences (CW) (http://www.nwo.nl/en/funding/research+funding)
2012/8	**Invited Reviewer**, The Wellcome Trust Fund, Sir Henry Wellcome Fellowship, London, UK (http://www.wellcome.ac.uk/Funding/Biomedical-science/Funding-schemes/Fellowships/Basic-biomedical-fellowships/wtx033549.htm)
2012-	**Associate Editor and Editorial Board Member** of BMC Pharmacology and Toxicology http://www.biomedcentral.com/bmcpharmacoltoxicol/about/edboard *(Impact factor*: 3.15)
2012	**Invited Grant Judge** of Intel International Science and Engineering 2012 (http://www.societyforscience.org/intelisef2012)
2011	**Invited Guest Editor** of *American Association of Pharmaceutical Scientists (AAPS) Journal*, 2011 Theme Issue "New Paradigms in Pharmaceutical Sciences: In Silico Drug Discovery". www.pharmagateway.net/ThemedIssuePage.aspx?JournalID=12248&CategoryID=1231 (*Impact factor*: 5.714)
2011 – 2015	**Charter Member** of NIH Biophysics of Neural Systems (BPNS) Study Section Review Panel (http://internet.csr.nih.gov/Roster_proto1/member_roster.asp?srg=BPNS&SRGDISPLAY=BPNS&CID=103011)
2011/7 -	**Editorial board Member** of American Journal of Molecular Biology www.scirp.org/journal/EditorialBoard.aspx?JournalID=532 .
2010/6	**Invited International Expert Reviewer** of Research Grant for the Molecular and Cellular Medicine Board (MCMB), Medical Research Council (MRC) Foundation, United Kingdom (http://www.mrc.ac.uk/Sciencesociety/MRF/index.htm)
2010/5	**Session chair/invited speaker**, International Medicinal Chemistry Symposium, Beijing, China (http://www.bitlifesciences.com/icm2010/default.asp)
2010/2	**Ad hoc Reviewer** of NIH Macromolecular Structure and Function D Study Section (MSFD) review panel
2010/2	**Invited Special Emphasis Panelist** for NIH National Institute on Drug Abuse (NIDA), "Targeted Library Synthesis and Screening at Novel Targets for Potential Drug Addiction (R21/R33)" (ZDA1 MXL-F)
2009/12	**Invited International Assessment Panelist** for Fudan University College of Pharmacy (one of the five international IAP members).
2009/10	**Invited External Reviewer** for Faculty Promotion in Jordan Applied Science Private University, Amman, Jordan

2006-2011	**Invited Expert Panel Reviewer** for Chinese Natural Sciences Foundation (CNSF) grant review panel meeting for Pharmaceutical Sciences Program, Beijing, China
2007-	***Ad hoc* Reviewer** of NIH Biomedical Library and Informatics Review Committee (BLIRC), National Library of Medicine
2006-	**Member** of NIH grant Center for Scientific Review *Biophysical and Biochemical Science Study Section* (ZRG1 F04B)
2008- 2010	**Chair** of the Graduate Admission Committee, and a member of Graduate Program Council, School of Pharmacy, University of Pittsburgh.
2008/10	**Chair** and **invited speaker**, 2008 International Drug Discovery and Technology Symposium: "GPCR Technology and Drug Discovery", Beijing China. (http://www.iddst.com/iddst2008/ScientificProgram.htm)
2008-	**Chair** of the Distinguished Lecture Series Committee, School of Pharmacy, University of Pittsburgh.
2008	**Committee Panel Meeting**, invited to NIH MLSCN Steering Committee Meeting, Albuquerque, NM
2008	**Advisory Panel Meeting**, invited to NIH Roadmap Committee Meeting: Defining the Role of Informatics within the Molecular Libraries Program (MLP), Bethesda, MD
2007-	**PI and Director** organizing NIH X02 PAR-07-353 CRC Center Grant – a collective cross-campus and cross-institution initiative to build Pittsburgh Cheminformatics Research Center (UPitt, PSC, and CMU) http://grants1.nih.gov/grants/guide/pa-files/PAR-07-353.html)
2006-	**Committee member and Co-PI** of NIH funded Pittsburgh Molecular Library Screening Center (PMLSC) and Drug Discovery Institute (DDI)
2006(10/19-22)	**Chair** and a leading organizer for 2006 American Chemical Society (ACS) Southwest Regional Meeting – NMR Symposium "Challenges of NMR Structural Proteomics", Houston, Texas.
2006(5/21-5/23)	**Faculty Chair** and an organizer for the 2006 MALTO meeting – Medicinal Chemistry and Pharmacognosy meeting at Houston, Texas.
2005-2006	**Member of the Board of Directors** of the Chinese Association of Professionals in Science and Technology (CAPST)(中国旅美专家协会) and a **Chairperson** of the CAPST-Biomedical and Pharmaceutical Society(医药生物工程学会).
2004-2006	**Member of the Advisory Steering Committee** for NIH Pharmacoinformatics Training Program at Houston – Gulf Coast Consortia
2004-2006	**Member of the Curriculum Committee** for the College of Pharmacy University of Houston, Texas
2004-	**Member** of the International Structural Genomics & Rationale Drug Design on Membrane Proteins Consortia (Dr. Kenneth Lundstrom), Switzerland
2004-2006	**Committee Member** for development of the Clinical Track Faculty Policy, College of Pharmacy, University of Houston

2004-2006	**Committee Member** of Information Technology, College of Pharmacy, University of Houston
2004- 2006	**Director** of Chemistry Coordinating Center – Chemistry Unit of the new GCC initiative – Chemical Genomics Screening Center Houston
2004-2006	**Informatics Advisory Committee member** of GCC Regional Small Molecules Library Screening Center, Houston
2004-2006	**Committee member** of Keck NMR Facility, University of Houston
2004	**Dept Chair Search Committee Member**, PPS, College of Pharmacy, UH, Houston
2001-2003	***Ad Hoc* Reviewer**, intramural grant University of Connecticut
2002/3	***Ad Hoc* Reviewer**, NIH, Cutting Edge Basic Research Award (CEBRA) Program
2001-	***Ad Hoc* Reviewer**, Peer-review Journals, Journal of Biophysics, Biochemistry, Proteins, Protein Expression and Purification, J. Medicinal Chemistry, Life Science, J. Peptide Research etc.);
2002	**Consultant,** Boston Scientific Corp, Natick, MA.
2000	**Consultant**, Pfizer Company, Groton, CT
2001	**Consultant**, Arch Chemical, Inc., Cheshire, CT
1999	**Consultant**, Roger Chemical Company, Norwich, CT.
1998	**Consultant**, Jeneric/Pentron Inc., Wallingford, CT
1998	**Consultant**, Uniroyal Chemical Co. Inc., Middlebury, CT
1997	**Consultant**, Enthone - OMI Inc., New Haven, CT

HONORS AND AWARDS

2017/10	**Nomination** of Chancellor's Outstanding Research Award， University of Pittsburgh
2017/9	**Final Award**, Sino-American Pharmaceutical Professional Association (SAPA) Venture Summit Roadshow Competition
2017/5	**Final Award**, Joint US Silicon Valley-China JiaShan Second Global Innovation AI computing Competition
2015/6	**Distinguished Alumni** invited to attend Second Military Medical University Graduation Commencement, Shanghai, China
2014/11	**Outstanding Research Achievement Award of American Association of Pharmaceutical Sciences (AAPS)** in Drug Discovery and Development Interface (Allergan)

2013/10	**XieHe Scholar Honorary Professor**, Chinese Academy of Medical Sciences & Peking Union Medical College
2012/9	**Exemplary Service Award** in NSF Fellowship Computational Biology Undergraduate Research Program
2006	**Nominee for 2006 Research Excellence Award** at University of Houston Texas
2005	**Top 20 popular articles award** (Protein Exp & Purif.). Elsevier Sciences Journal Editor： "this award recognized the popularity and interests/values of your research work to the others in the field over 10 million registered online users").
2005	**Best Poster Presentation Award** (graduate student W.Y. Sheng) – 2005 MALTO Meeting, Oxford, MS.
2003	**Nominated for Outstanding Faculty Advisor Award**, University of Connecticut
1998-2003	**NIH FIRST Award**, NIH NIDA
1999	**Chinese Government Natural Science Foundation (CNSF) Award**
1999, 2001	**North America China Bridges International (CBI) Award**
1998	**Chinese Government Educational Bureau Foundation Award**
1994, 1995	**NSF Research and Education Fund** Program for Faculty Enhancement
1994, 1996	**Minority Staff Development Fund Program Award,** University of Connecticut
1992	**An elected Member of *PHI KAPPA PHI* Honor Society**, University of Connecticut
1991	***Summa cum laude honor* Award** for academic excellence, University of Connecticut
1991	**Special Achievement Award** for NMR Facility Service, University of Connecticut
1984	**Outstanding Teaching Award**, the Second Military Medical University, Shanghai, P. R. China

CONTINUED EDUCATIONS

Shared Leadership Cohort Development Experience (John C. Porcari, JPorcari & Associates LLC)
Leadership Training Workshop (June – December, 2011). To develop our shared vision and creating goals and strategies through long-range planning. To learn concepts of how interpersonal dynamics affect our abilities to achieve individually and as a group. To compassionate presence, asset based thinking, proactive/reactive life orientation, and drama to empowerment.

Advanced Computer and Database TRAINING:

- IRIX Advanced Administration Training Course, 1999, Silicon Graphic, Inc. • Daylight Cheminfo Database Construction, Use and Management - Summer Training, 1999 Daylight Chemical Information, Inc. Sante Fe, New Mexico,

Advanced NMR training:

• NMR Electronics/Trouble Shooting, March, 1994; • Faculty Enhancement Program & NMR Concepts, July 1994 (NSF Program); • Faculty Enhancement Program & NMR Concepts, Aug. 1995 (NSF Program); • Bruker AVANCE-I and -II, AVANCE Service & Maintenance, and Solid-state NMR Courses, 1996 (Bruker Inst. Inc.).

Advanced Protein Biochemistry Training:

"Drug Discovery Using Molecular Biology Techniques to Find Drug Targets" Boston, MA 2000 (ACS Workshop)

Advanced HTPS Course:

Advanced High Throughput Screen for New Drug Discovery Course
Joint academic-industrial course, Storrs, University of Connecticut 1995

News and Press Release about Xiang-Qun (Sean) Xie's research and technologies

- June 22, 2014 at 2:57 pm **"*TargetHunter*"**
  http://www.pages.pharmacy.pitt.edu/epittpharmacy/2014/06/22/target-hunter/

- PITTPHARMACY Spring 2014 "***LEADING → THE Way: Xie's lab matches molecules to disease states at warp speed*"**
  http://www.pages.pharmacy.pitt.edu/publications/wp-content/uploads/sites/25/2014/05/PittPharmacy_Spring2014.pdf

B. PUBLICATIONS

PATENTS AND PATENT DISCLOSURE FILED:

1) **Xie, X-Q*.**, J.Z. Chen and Y.X. Zhang. "Ligands Specific for Cannabinoid Receptor Subtype 2". Patent No: **US8466131 B2**, Application No. US 12/740,099; PCT No: PCT/US2008/012395; Publication date: Jun 18, 2013; Filing date: Oct 31, 2008. https://www.google.com/patents/US8466131?dq=20110118214

2) **Xie, X-Q*.**, J.Z. Chen and Y.X. Zhang. "Ligands Specific for Cannabinoid Receptor Subtype 2". Publication No: **US20110118214 A1**, Application No. US 12/740,099; PCT No: PCT/US2008/012395; Publication date: May 19, 2011; Filing date: Oct 31, 2008.

3) **Xie, X-Q*.**, J.Z. Chen and Y.X. Zhang. "Ligands Specific for Cannabinoid Receptor Subtype 2". Publication No: **WO2009058377 A1,** Application No. PCT No: PCT/US2008/012395; Publication date: May 7, 2009; Filing date: Nov 1, 2007.

4) **Xie, X-Q*.,** Myint, K., Kurihara, N., Roodman, D. "P62-ZZ Chemical Inhibitor" (This is the first p62 chemical inhibitor with therapeutic potential for multiple myeloma). Publication No**: US 20150175607 A1** (Application No.US No14/237,494); PCT Publication No: WO2013022919 A1 (Application No: PCT/US2012/049911). **Xie, X-Q*.** Provisional USSN 61/521,287. Filing date: Aug 8, 2012; Publication date: June 25, 2015.) Publication No: CN103930166 A (Application No: CN 201280048718). *The patents above had been transferred to XQ XIE, ID4Pharma LLC under the signed patent licensing agreement between University of Pittsburgh and ID4Pharma LLC on March 27, 2014. The patents were further licensed out to Oxis Biotech Company on Dec 31, 2014.

   http://www.google.com/patents/US20150175607?cl=en

5) **Xie, X-Q*.,** Myint, K., Kurihara, N., Roodman, D. "P62-ZZ Chemical Inhibitor" (This is the first p62 chemical inhibitor with therapeutic potential for multiple myeloma). Publication No: **US 20150175607**

A1, Application No.US 14/237,494, PCT/US2012/049911, Publication date: June 25, 2015, Filing date: Aug 8, 2012.(Pitt No. 02454)

6) **Xie, X-Q*,** Myint, K., Kurihara, N., Roodman, D. "P62-ZZ Chemical Inhibitor" (This is the first p62 chemical inhibitor with therapeutic potential for multiple myeloma). Publication No: **WO2013022919** A1, PCT/US2012/049911, Publication date: Feb 14, 2013, Filing date: Aug 8, 2012; Provisional USSN 61/521,287.

7) **Xie, X-Q*** "P62-ZZ Chemical Inhibitor" (This is the first p62 chemical inhibitor with therapeutic potential for multiple myeloma). Publication No: **CN103930166 A**, Application No: CN 201280048718, PCT No: PCT/US2012/049911; Publication date: June 16, 2014. Filing date: Aug 8, 2012.

8) **Xie, X-Q.*,** Feng, RT, and Peng Yang "Preparation of phenylacetamide compounds as cannabinoid receptor 2 (CB2) inverse agonists and therapeutic potential for multiple myeloma and osteoporosis bone diseases". Patent No. **US 8772541 B2** (Appl No: 13/715603, Publication date: July 8, 2014); Patent No. US20140296294 A1 (Appl No: 14/305,941. Filing date: 06/16/2014); US20130172388 A1 (Appl No: US 13/715,603, Filing date: 12/14/2012) ; Provisional US Application No: 61/576,041; Pitt No: 02549. https://www.google.com/patents/US8772541?dq=US+8772541

9) **Xie, X-Q.*,** Feng, RT, and Peng Yang "Cannabinoid receptor 2 (CB2) inverse agonists and therapeutic potential for multiple myeloma and osteoporosis bone diseases" Patent No. **US 8772541 B2**; Appl No: 13/715603; Publication date: July 8, 2014.

10) **Xie, X-Q.*,** Feng, RT, and Peng Yang "Novel cannabinoid receptor 2 (cb2) inverse agonists and therapeutic potential for multiple myeloma and osteoporosis bone diseases" Patent No. **US20140296294 A1**; Appl No: 14/305,941; Filing date: Jun 16,2014.

11) **Xie, X-Q.*,** Feng, RT, and Peng Yang "Novel cannabinoid receptor 2 (cb2) inverse agonists and therapeutic potential for multiple myeloma and osteoporosis bone diseases" **US20130172388 A1**; Appl No: US 13/715,603, Filing date: Dec 14, 2012); Provisional US Application No: 61/576,041; Pitt No: 02549

*****the three patents above are successfully licensed to biotech company in the US.**

(new filing)

12) Xie X-Q, "p18 inhibitors and use thereof". US Provisional Patent Application No. 62/295,696

13) Xie X-Q: WIPO PCT WO2016/200827 A1: "p62-ZZ CHEMICAL MODULATORs". Filed on June 11, 2016. New provisional patent application No. 62/174,465* This is new anti-MM p62ZZ small molecule patent filed under a new patent. (Pitt No.: 03577)

14) Cheng, T, Xie, XQ, and Gao, YD "p18 small molecule chemical inhibitor and human hematopoietic stem cell expansion ex vivo". 专利号 Patent No. 201510081641. Publication No: 2015061001183450. Classification No. C07C303/38(2006.01) (300457). 2015-06-12, 17:27 (http://www.aptchina.com/zhuanli/11599713/).

15) **Xie, X-Q.*,** Feng Z. Human transient receptor potential vanilloid type 1 (hTRPV1) Chemical Agents. PCT/US2016/016826 Pitt Ref.: 03491. Attorney Ref.: 076333-0673. Application No.: 62/113,429

16) **Xie, X-Q**.*, Yang P, Almehizia A. Novel Cannabinoid Receptor CB2 Ligand 4-(aminomethyl)- N,N-diethylanilines. U.S. Patent Application No. 62/181,695, F&L Ref.: 076333-0549, (Pitt Ref No.: 03493), June 18, 2015.

17) Gold, B. and **Xie, X-Q**, Srinivasan, A and Wang, L.R. "Compounds and Methods for Inhibition of AP endonuclease-1/redox factor-1 (hAPE1) activity." International Appl No.: PCT/US2013/023653, WO2013/116228; USSN: 61/593,276, Pitt Ref. No. 02385

18) Yin, XM and **Xie, X-Q**, "Modulation of Autophagy by Atg4B inhibitors" Int. Reference 02204 (patent pending).

19) **Xie, X-Q**, Mu, Ying and Xie, ZJ "CD1X on Dendritic Cells: A Novel Biomarker of Metallic Allergens and Metallic Non-Allergens". Int. Reference 03156 (Patent Pending).

PEER-REVIEWED PUBLICATIONS: (SciFinder search name: Xiang-Qun Xie, Xiang Qun Xie, Xiangqun Xie, or Xiang-Qun (Sean) Xie， or XQ Xie, X.-Q. Xie)

(2018)

1. Yoo YD; Mun SR; Ji CH; Sung KW; Kang KY; Heo AJ; Lee SH; AN JK, HWANG J, **Xie X-Q;** Ciechanover A; Kim BY and Kwon YT. **N-terminal arginylation generates a bimodal degron that modulates autophagic proteolysis. *PNAS*** March 5, 2018. 201719110; https://doi.org/10.1073/pnas.1719110115

2. Adamik J, Silbermann R,, Marino S, Sun, QH, Anderson JL, Dan Zhou D, Xie X-Q, Roodman, GD and Galson, DL, **XRK3F2 Inhibition of p62-ZZ Domain Signaling Rescues Myeloma-Induced GFI1-Driven Epigenetic Repression of the Runx2 Gene in Pre-osteoblasts to Overcome Differentiation Suppression.** Front. Endocrinol., 29 June 2018, volume 9, article 334 https://doi.org/10.3389/fendo.2018.00344
The XRK3F2 was discovered and sysnthesized by Xie's lab. The studies confirmed that XRK3F2 exhibits promising anti-multiple myeloma and anti-osteoclast by blocking p62-ZZ domain-dependent signaling. XRK3F2 can reverse epigenetic-based mechanisms of MM-induced *Runx2* suppression and promote osteogenic differentiation.

3. Cha-Molstad, H, Kim JG, Hwang, J, Kim BY, Lee SH, Sung KW., Shim SM, Ganipisetti, S, Ciechanover, A, Kwon YT, Kim JG, Kim BY, McGuire, T, **Xie, X-Q*,** Mook-Jung, I*, Ciechanover, A*, Kwon YT*, **Regulation of autophagic proteolysis by the N-recognin SQSTM1/p62 of the N-end rule pathway**. ***Autophagy***. 2018;14(2):359-61. doi: 10.1080/15548627.2017.1415190. PubMed PMID: 2018:224510.
*Xie lab discovered and designed first p62ZZ chemical probe that was used to investigate macroautophagy mechanism of mediating the selective degradation of proteins and non-proteinaceous cellular constituents. This is a joint research efforts with scientists at National Seoul University.

1) Xue, Y.; Feng, Z.-w.; Li, X.-y.; Hu, Z.-h.; Xu, Q.; Wang, Z.; Cheng, J.-h.; Shi, H.-t.; Wang, Q.-b.; Wu, H.-y.; **Xie, X.-Q.*;** Lv, Q.-Z.*, "The efficacy and safety of cilostazol as an alternative to aspirin in Chinese patients with aspirin intolerance after coronary stent implantation: a combined clinical study and computational system pharmacology analysis." ***Acta Pharmacologica Sinica*, 2018**, 39, 205-212. doi: 10.1038/aps.2017.85
*We carried out, in collaboration with ZhongShan hospital in China, a combined clinical study and computational system pharmacology analysis to study the efficacy and safety of cilostazol as an alternative to aspirin in Chinese patients with aspirin intolerance after coronary stent implantation. We conclude that in the patients with aspirin intolerance undergoing coronary stent implantation, the combination of clopidogrel with cilostazol may be an efficacious and safe alternative to the standard DAT regimen.

4. Cha-Molstad H, Yu Ji E, Kim Jung G, Hwang J, Ganipisetti S, Lee Kyung H, Kim Bo Y, Yu Ji E, Hong Jin T, Feng Z, Yang P, McGuire T, Wang N, Jang Jun M, Ciechanover A, Inhee MJ, Kwang PK, **Xie X-Q***, Kwon YT*, & Kim, BY*. **p62/SQSTM1/Sequestosome-1 is an N-recognin of the N-end rule pathway which modulates autophagosome biogenesis**. ***Nat Commun.*** 2017;8(1):102. PMID: 28740232. DOI:10.1038/s41467-017-00085-7

(2017)

2) Bian, Y., Feng, Z., Yang, P., & **Xie, X. Q.*** (2017). **Integrated In Silico Fragment-Based Drug Design: Case Study with Allosteric Modulators on Metabotropic Glutamate Receptor 5**. *AAPS J* **(2017)** 19: 1235-1248. https://doi.org/10.1208/s12248-017-0093-5 PMID: 27810775
*Xie lab has constructed fragment-based allosteric modulators chemogenomics knowledgebase to facilitate new allosteric functional ligands. First, a set of integrated computational methodologies was first used by combining fragment library generation and retrosynthetic combinatorial analysis procedure (RECAP) for novel compound generation. Then, the compounds generated were assessed by benchmark dataset verification, docking studies, and QSAR model simulation. Subsequently, structurally diverse compounds, with reported or unreported scaffolds, can be observed from top 20 in silico synthesized compounds, which were predicted to be potential functional modulators. In silico compounds with reported scaffolds fill SAR holes in known, Our case study of designing allosteric modulators on mGlu5 demonstrated that the established computational fragment-based approach is a useful methodology for facilitating new compound design in the future.

3) Cha-Molstad H, Yu JE, Feng ZW, Lee SH, Kim JG, Yang P, Yoo YD, Hwang, JS, McGuire T, Shim SM, Song HD, Wang NZ, Jang MM, Lee MJ, Kim SJ, Ciechanover A, Mook-Jun I, **Xie* XQ**, Yong Tae Kwon*, and Bo Yeon Kim* **"**p62/SQSTM1/Sequestosome-1 is an N-recognin of the N-end rule pathway which modulates autophagosome biogenesis**"** ***Nature Comm.*** 2017; 8(1), 102. PMID: 28740232. doi:10.1038/s41467-017-00085-7 **(Xie is a co-correspodent author)**
*Xie lab discovered and designed first p62ZZ chemical probe that was used to investigate macroautophagy mechanism of mediating the selective degradation of proteins and non-proteinaceous cellular constituents. This is a joint research efforts with scientists at National Seoul University. The results show that the N-end rule pathway modulates macroautophagy. In this mechanism, the autophagic adapter p62/SQSTM1/Sequestosome-1 is an N-recognin that binds type-1 and type-2 N-terminal degrons (N-degrons), including arginine (Nt-Arg). Both types of N-degrons bind its ZZ domain. The results suggest that p62 is a key molecule in the crosstalk between the ubiquitin-proteasome system (UPS) and autophagy. The outcome of our innovative work provides a significant insight into new neurodisordor drug research through better understanding that the functional proteins lose their folding through post-translational conjugation (e.g., hyperphosphorylated tau in Alzheimer's disease), endoproteolytic cleavage (e.g., amyloid β), and genetic mutations (e.g., huntingtin in Huntington's disease (HD), or various stresses).

4) Si Chen, Zhiwei Feng, Yun Wang, Shifan Ma, Ziheng Hu, Peng Yang, Yifeng Chai and Xiang-Qun Xie*. "Discovery of Novel Ligands for TNF-α and TNF Receptor-1 through Structure-Based Virtual Screening and Biological Assay". ***J Chem Inf Model***. 2017 May 22;57(5):1101-1111, DOI: 10.1021/acs.jcim.6b00672. PMID: 28422491

*TNF-α is an important cytokine with powerful proinflammatory and immunomodulatory effects. Overexpression of TNF-α is shown in HIV, asthma, and in autoimmune diseases, such as rheumatoid arthritis, Crohn's disease and psoriasis. _ENREF_7TNF-α is an important therapeutic target for autoimmune diseases with the successful launch of TNF-α antagonists, including infliximab, etanercept, adalimumab, certolizumab and glolimumab. However, there exist inevitable shortcomings of these biologic therapies, such as increased risk of infection, high cost and requirement for intravenous injections. By comparison studies, new small molecule inhibitors were screened in silico and also confirmed by in vitro bioassays. Such new small molecules are cost-effective to synthesis and water-soluble, and the 3D models can be used to identification of small molecules specific to inhibit TNF-α regulated pathways with potential therapeutics.

5) Nanyi Wang, Lirong Wang* and **Xiang-Qun Xie*,** "ProSelection: A Novel Algorithm to Select Proper Protein Structure Subsets for in Silico Target Identification and Drug Discovery Research", ***Journal of Chemical Information and Modeling*** 2017, 57(11):2686-2698. PMID: 29016123 DOI: 10.1021/acs.jcim.7b00277

Wang, Nanyi (2017) "Computational approach for autophagy and apoptosis specific knowledgebases-guided system pharmacology drug research". Master's Thesis, University of Pittsburgh.
*Xie Lab developed a new algorithm, ProSelection, and implemented it into its chemogenomics database to facilitate users select the proper protein structures for their docking modeling and virtual screening drug design.

6) Zhang, Zhaojia (2017) Quantitative Simulation on Concentration-Time Profiles of Oxycodone Co-administration with Diazepam. Master's Thesis, University of Pittsburgh.

*Xie Lab has performed and established the quantitative simulation models on pharmacokinetic profiles of oxycodone and its high-risk drug-drug interaction, such as with diazepam. With such analytical predicting models, we can predict the threshold of potential prescription-opioid overdose and provide caution instruction to MD clinicians for the rational drug uses to avoid prescription opioid overdose.

(2016)

7) Xu XM, Ma SF, Feng ZW, Hu GX, Wang LR*, and **Xie XQ*.** "Chemogenomics Knowledgebase and Systems Pharmacology for Hallucinogen Target Identification - Salvinorin A （Salvia divinorum 墨西哥鼠尾草） as a Case Study", ***Journal of Molecular Graphics and Modelling***, 2016; 70 (11): 284-295. doi: 10.1016/j.jmgm.2016.08.001. Epub 2016 Aug 8. PMID: 27810775

* Xie Lab has constructed the first Hallucinogen Chemogenomics Database (www.CBLigand.org/Hallucinogen) by integrating the chemogenomics tools to study interactions between hallucinogens chemicals/substances and related proteins. We predicted that there are four novel targets for salvinorin A, including muscarinic acetylcholine receptor 2, cannabinoid receptor 1, cannabinoid receptor 2 and dopamine receptor 2. Overall, our Chemogenomics knowledgebase provides the enriched knowledge information resources for systems pharmacological analysis, target identification and drug discovery for hallucinogens.

8) **Xie XQ***, Wang LR, Wang JM, Xie ZJ, Yang P, and Ouyang Q. "In Silico Chemogenomics Knowledgebase and Computational System Neuropharmacology Approach for Cannabinoid （大麻受体）Drug Research" ***Neuropathology of Drug Addictions and Substance Misuse***, 2016, Volume 3, chapter 19. 183-195. 10.1016/B978-0-12-800634-4.00019-6. Copyright © 2016 Elsevier Inc.

*XIE Lab began in 1995 to construct cannabinoid molecular information database (CBID). Then further expand it into drug abuse database to cover all aspects of drug addictions and substance misuses

9) Zhang Y, Wang, LR, Cheng HZ, Ding YH, Feng ZW, Cheng T, Gao YD and **Xie XQ*** "StemCellCKB: An Integrated Stem Cell-Specific Chemogenomics Knowledge base for Target Identification and Systems-Pharmacology Research", ***J Chem Inf Model.*** 2016, 56 (10), pp 1995–2004 DOI: 10.1021/acs.jcim.5b00748

*Xie's lab has developed Stem Cell Chemogenomics Database (StemCellCKB, www.CBLigand.org/StemCellCKB) and applied it to investigate hematopoietic stem cell signaling and drug research for system pharmacology and mechanism studies.

10) Zhang H, Ma SF, Feng ZW, Wang DY, Li CJ, Cao Y, Chen XF, Liu AJ, Zhu ZY, Zhang JP, Zhang GQ, Chai YF*, Wang LR* and **Xie XQ*** "Cardiovascular Disease-specific Chemogenomics Knowledgebase-guided Target Identification and Drug Synergy Mechanism Study of A Combination of an Herbal Formula." (Nature) ***Scientific Reports***, 2016 Sep 28;6:33963. doi: 10.1038/srep33963. PMID:27678063

*Xie's lab has developed a first Cardiovascular Disease (CVD) database and applied it to investigate the Traditional Chinese Medicine formulae for system pharmacology and mechanism studies of combinational therapy. 发表计算化学基因组学智能库和药物靶点及系统药理研究传统中药付方 "四逆汤"（IF=4. 259）

11) Zhang H, Sun S, Zhang W, Xie X, Zhu Z, Chai Y, Zhang G. Biological activities and pharmacokinetics of aconitine, benzoylaconine, and aconine （乌头碱，苯甲酰乌头碱和乌头碱）after oral administration in rats. *Drug Testing and Analysis*. 2016;8(8):839-46. doi: 10.1002/dta.1858.

12) **Xie* X-Q**, Feng Z, inventors; (University of Pittsburgh - of the Commonwealth System of Higher Education, USA). assignee. Preparation of N,N'-diphenyl ureas and related as hTRPV1 inhibitors (辣椒素受体). Application: WO *patent* 2016-US16826; 2016127085. 2016 20160205.

*We have identified a series of diarylurea analogues for hTRPV1 with both inverse agonists and agonist. We also designed the drug-like "hybrid" compounds for both TRPV1-CB2 (~800nM) as the non-addictive alternatives. We provide novel strategies to develop a small-molecule inhibitor to simultaneously target two or more inflammation-related proteins for the treatment of a wide range of inflammatory disorders including neuro-inflammation and neurodegenerative diseases with potential synergistic effect.

13) Wang L, **Xie* X-Q**. Cancer genomics: opportunities for medicinal chemistry? *Future Medicinal Chemistry*. 2016;8(4):357-9. doi: 10.4155/fmc.16.1.

14) Teramachi J, Silbermann R, Yang P, Zhao W, Mohammad KS, Guo J, Anderson JL, Zhou D, Feng R, Myint KZ, Maertz N, Beumer JH, Eiseman JL, Windle JJ, **Xie* XQ**, Roodman* GD, Kurihara* N. Blocking the ZZ domain of sequestosome1/p62 suppresses myeloma growth and osteoclast formation in vitro and induces dramatic bone formation in myeloma-bearing bones in vivo. *Leukemia* (Nature) 2016;30(2):390-8. doi: 10.1038/leu.2015.229.

* Xie's lab was the ***first*** to discover and develop p62ZZ chemical inhibitors with promising anti-multiple myeloma (MM) therapeutic index (Patent: Xie et al ***USSN 61/521,287, PCT/US2012/049911)*** in collaboration with Dr. David Roodman. Our innovation is based on the therapeutic knowledge and our data that the Sequestosome-1 (or p62) plays critical roles in the survival, growth and metastasis of MM cells. P62 is a key domain activating NF-κB, and p38 MAPK, both of which are aberrantly activated in MM, thus it is a promising drug target for MM treatment. We have proved that the ZZ domain of p62 is responsible for increased MM cell growth and osteoclast (OCL) formation mediated by NF-κB and p38 MAPK signaling. Our discovered lead compound XIE3P62ZZ **(#3** or **XRK3,** 4.31 μM) exhibited notable p62 antagonistic effects and significantly reduced survival of human MM cells and also inhibited osteoclastogenesis. **The specificity was further confirmed by p62$^{-/-}$ experiments**, in which effects of the inhibitor XRK3 on MM cells and tumor necrosis factor (TNF)-α-induced osteoclast (OCL) formation were lost upon p62$^{-/-}$ gene deficiency.

The most recent development of our preliminary chemistry modification of this lead produced more potent p62 inhibitor analogs (e.g., **XIE1-10b**: IC_{50} 1.12, **XIE1-62a**: 0.63 μM) with improved drug-like properties ($t_{1/2}$ = 4.5 hrs, Bioavailability 43%). The ***in vivo*** MM xenograft murine model revealed significantly inhibited MM tumor growth (>75%) and increased mean survival time (53%) compared with the control group. This will be reported in Nature Scientific Reports.

15) Hu J, Hu J, Hu Z, Zhang Y, Wang L, Xie **X-Q**, Hu J, Gou X, Mu Y, Wang L, **Xie* X-Q**. Metal binding mediated conformational change of XPA protein:a potential cytotoxic mechanism of nickel in the nucleotide excision repair. *Journal of molecular modeling*. 2016;22(7):156. doi: 10.1007/s00894-016-3017-x. Epub 2016 Jun 16

* This is a joint project under the consortium between University of Pittsburgh and FDA. XIE lab has carried out 3D protein modeling to predict metal and protein interaction in order to understand allergy caused metal allergens, such as nickel etc. The computational data will be used to guide the experimental validation studies conducted by Dr Yin Mu at FDA under FDA/PITT consortium.

16) Hu J, Feng Z, Ma S, Zhang Y, Tong Q, Alqarni MH, Gou X, **Xie* X-Q**. Difference and Influence of Inactive and Active States of Cannabinoid Receptor Subtype CB2 （大麻受体 CB2）: From Conformation to Drug Discovery. *Journal of Chemical Information and Modeling*. 2016;56(6):1152-63. doi: 10.1021/acs.jcim.5b00739. PMID:27186994.

* The cannabinoid receptor 2 (CB2) plays an important role in the immune system. Although a few of GPCRs crystallographic structures have been reported, it is still challenging to obtain functional transmembrane proteins and high resolution X-ray crystal structures, such as for CB2 receptor. Xie Lab has carried out extensive 3D modeling studies of CB2 activation signaling mechanism by using CB2 agonist and CB2 inverse agonist to

investigate the CB2 receptor structure in the inactive and active states. Our computational work will facilitate the research on cannabinoid ligand design.

17) Feng Z, Pearce LV, Zhang Y, Xing C, Herold BKA, Ma S, Hu Z, Turcios NA, Yang P, Tong Q, McCall AK, Blumberg PM, **Xie* X-Q**. Multi-Functional Diarylurea Small Molecule Inhibitors of TRPV1 (辣椒素受体) with Therapeutic Potential for Neuroinflammation. *AAPS Journal*. 2016;18(4):898-913. doi: 10.1208/s12248-016-9888-z. PMID:27000851.

(Patent) Xie, X-Q., Feng Z. hTRPV1 Chemical Agents. Pitt Ref No.: 03491, 2016
*Transient receptor potential (TRP) channels are among the largest families of ion channels. TRPV1 has been reported to contribute to acute and chronic pain, such as osteoarthritis, neuropathic pain, migraine, inflammatory bowel disease, and bone cancer pain. Brain TRPV1 is also postulated to have a pathogenic role in various neurological and psychiatric disorders, ranging from Parkinson's disease, schizophrenia, and Alzheimer's disease to anxiety, depression, and other mood disorders. Xie Lab has established 3D TRPV1 strucuture model and predicting pockets, which were used to discover novel lead compounds for hTRPV1in collaboration with Dr Peter Blumberg at NIH.

18) Yan Zhang, Lirong Wang and **Xiang-Qun Xie*.** "*Kinetic Modelling of Cannabinoid Receptor Type 2 Endocytosis and Trafficking*". 2016, *Molecular BioSystems*, submitted and Zhang, Yan (2016) "*Mathematical Modeling of Cannabinoid Receptor Type 2 Endocytosis and Trafficking"*, Master's Thesis, University of Pittsburgh.

* A fully developed math simulation model validated and calibrated by experimental data would allow us to predict how variations of the a GPCR cell signaling system could change its response to ligand treatment, such as cannabinoid CB2 receptor and its ligands. It is known that disease conditions, intervention from other pathways, as well as cell expression profile in different tissues, can change the abundance of certain proteins or small molecules.

(2015)

19) **Xie* X-Q**, Yang P, Zhang Y, Zhang P, Wang L, Ding Y, Yang M, Tong Q, Cheng H, Ji Q, McGuire T, Yuan W, Cheng T, Gao Y. Discovery of novel INK4C small-molecule inhibitors to promote human and murine hematopoietic stem cell ex vivo expansion. *Scientific Reports*. 2015;5:18115. doi: 10.1038/srep18115.

* Xie Lab discovered INK4C targeted small-molecules in his previously published 2014 *Nature Comm*. In this Sci Reports paper, we showing stimulate both murine and hyman hematopoetic stem cells ex vivo. (Impact Factor IF=5.228)

20) Myint KZ, **Xie* X-Q**. Ligand Biological Activity Predictions Using Fingerprint-Based Artificial Neural Networks (FANN-QSAR). *Methods in Molecular Biology (New York, NY, United States)*. 2015;1260(Artificial Neural Networks):149-64. doi: 10.1007/978-1-4939-2239-0_9.

21) Ji K-L, Zhang P, Li X-N, Guo J, Hu H-B, Xiao C-F, **Xie* X-Q**, Xu Y-K. Cytotoxic limonoids from Trichilia americana leaves (美国的鹧鸪花属 Trichilia 叶子). *Phytochemistry (Elsevier)*. 2015;118:61-7. doi: 10.1016/j.phytochem.2015.08.014.

22) Gao* Y, **Xie* X**, Yang M, Li C, Ji Q, inventors; (Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences, Peop. Rep. China). assignee. One kind of drug-resistant multiple myeloma animal model and its construction method [Machine Translation]. Application: CN *patent* 2015-10223834 104830776. 2015 20150505.

23) Gao Y, Yang P, Shen H, Yu H, Song X, Zhang L, Zhang P, Cheng H, Xie Z, Hao S, Dong F, Ma S, Ji Q, Bartlow P, Ding Y, Wang L, Liu H, Li Y, Cheng H, Miao W, Yuan W, Yuan Y, Cheng* T, **Xie* X-Q**. Small-molecule inhibitors targeting INK4 protein p18INK4C enhance ex vivo expansion of haematopoietic stem cells. *Nature Communications*. 2015;6:6328. doi: 10.1038/ncomms7328.

*Xie's Lab has discovered a first small chemical molecule that inhibits $p18^{INK4C}$, a member of the cyclin-dependent kinase (CDK) inhibitors (CKI), and a potent negative regulator of human hematopoietic stem cells (HSC) self-renewal by using his developed computational chemical genomics screening approach and stem cells specific chemogenomics knowledgebase. The designed and synthesized p18-targeted small drug molecules are used as chemical probes to explore the mechanisms of activating HSC self-renewal in increasing the quantity of functional stem cells. Ultimately, our work is to developing HSC drugs for therapeutic uses. (Xie - Invited speaker, Nov 2012, " Novel Small Chemical Inhibitors Targeting p18INK4C Protein for Hematopoietic Stem Cell Expansion", 3rd International Forum on Stem Cells) (Patent)

24) Feng Z, Pearce LV, Xu X, Yang X, Yang P, Blumberg PM, **Xie* X-Q**. Structural Insight into Tetrameric hTRPV1 (辣椒素受体) from Homology Modeling, Molecular Docking, Molecular Dynamics Simulation, Virtual Screening, and Bioassay Validations. *Journal of Chemical Information and Modeling*. 2015;55(3):572-88. doi: 10.1021/ci5007189.

25) Feng Z, Ma S, Hu G, **Xie* X-Q**. Allosteric Binding Site and Activation Mechanism of Class C G-Protein Coupled Receptors: Metabotropic Glutamate Receptor Family. *AAPS Journal*. 2015;17(3):737-53. doi: 10.1208/s12248-015-9742-8.

*We studied the allosteric binding sites for G-Protein Coupled Receptors (GPCRs), especially for Class C and Class A. We provided new insight into better understanding of modulator and bitopic ligands with therapeutic potential and also summarizes the state-of-the-art computational methods for the discovery of modulators and bitopic ligands.

26) Feng Z, Kochanek S, Close D, Wang L, Almehizia Abdulrahman A, Iyer P, **Xie X-Q**, Johnston Paul A, Gold B, Srinivasan A. Design and activity of AP endonuclease-1 inhibitors. *Journal of chemical biology*. 2015;8(3):79-93.

* This is a collaboration project between Gold, Xie and Johnston. XIE Lab discovered and synthesized APE1 inhibitors, Dr Gold's lab carried out extensive bioassays studies and Dr Johston's lab did further anti-cancer drug data screening.

27) Feng Z, Hu G, Ma S, **Xie* X-Q**. Computational Advances for the Development of Allosteric Modulators and Bitopic Ligands in G Protein-Coupled Receptors. *AAPS Journal*. 2015;17(5):1080-95. doi: 10.1208/s12248-015-9776-y.

28) Feng R, Tong Q, Xie Z, Cheng H, Wang L, Lentzsch S, Roodman GD, **Xie* X-Q**. Targeting cannabinoid receptor-2 （大麻受体 CB2）pathway by phenylacetylamide suppresses the proliferation of human myeloma cells through mitotic dysregulation and cytoskeleton disruption. *Molecular Carcinogenesis*. 2015;54(12):1796-806. doi: 10.1002/mc.22251.

*Xie's lab is the first discovered novel Cannabinoid receptor CB2 ligands with new chemical scaffolds and also first report the new therapeutic application of CB2 ligands to human myltiple myeloma intervention (**US patent**: **Xie, X-Q.,** Myint, K., Kurihara, N., Roodman, D. "P62-ZZ Chemical Inhibitor and Therapeutic Potential for Multiple Myeloma" PCT/US2012/049911; WO2013/022919A1; USSN 61/521,287, Application No. 14/237,494, filed February 6, 2014).

29) Cheng* T, **Xie* X**, Gao* Y, Yang P, inventors; (Peop. Rep. China). assignee. Sodium 4-cyclohexylaminosulfonylbenzoate as p18 micromolecular inhibitor and its application in human

hematopoietic stem cell proliferation in vitro. Application: CN *patent* 2015-10081641 104693075. 2015 20150213.

(2014)

30) Zhu YB, Xie **XQ**, Li ZY, Bai H, Dong L, Dong ZP, Dong JG. Bioinformatic analysis of the nucleotide binding site-encoding disease-resistance genes in foxtail millet (Setaria italica (L.) Beauv.). *GMR, Genetics and Molecular Research*. 2014;13(3):6602-9, 8 pp. doi: 10.4238/2014.August.28.5.

31) Zhang S, Jia N, Shao P, Tong Q, **Xie X-Q**, Bai M. Target-Selective Phototherapy Using a Ligand-Based Photosensitizer for Type 2 Cannabinoid Receptor （大麻受体 CB2）. *Chemistry & Biology (Oxford, United Kingdom)*. 2014;21(3):338-44. doi: 10.1016/j.chembiol.2014.01.009.

32) Zeng D, Ouyang Q, Cai Z, **Xie X-Q**, Anderson CJ. New cross-bridged cyclam derivative CB-TE1K1P, an improved bifunctional chelator for copper radionuclides. *Chemical Communications (Cambridge, United Kingdom)*. 2014;50(1):43-5. doi: 10.1039/c3cc45928d. (journal coverpage)

* The article was selected by Editor-in-Chief as a coverpage of the journal. With collaborative research work by Dr. Anderson and Dr. Xie labs, innovative image material, CBTE1K1P, was developed and it can serve as an improved BFC for conjugation to small molecules, peptide and protein-based biomolecules, for labelling with ^{64}Cu or other copper radionuclides with applications in diagnostic imaging, radiotherapy, and/or theranostics.

33) **Xie* X-Q**, Wang L, Liu H, Ouyang Q, Fang C, Su W. Chemogenomics knowledgebased polypharmacology analyses of drug abuse related G-protein coupled receptors and their ligands. *Frontiers in Pharmacology (Neuropharmacology)*. 2014;5:1-11. doi: 10.3389/fphar.2014.00003.

*This is the first research article reported by Xie Lab about chemogenomics knowledge database and integrated polypharmacology analysis tools for GPCRs-related drug abuse targets and associated ligands. Such public knowledgebase will facilitate information exchange and new medicine design and discovery for treatment of drug abuse and addiction.

34) Wang N, Bartlow P, Ouyang Q, **Xie* X-Q**. Recent advances in antimultiple myeloma drug development. *Pharmaceutical Patent Analyst*. 2014;3(3):261-77. doi: 10.4155/ppa.14.18.

35) Wang L, **Xie* X-Q**. Computational target fishing: what should chemogenomics researchers expect for the future of in silico drug design and discovery? *Future Medicinal Chemistry*. 2014;6(3):247-9. doi: 10.4155/fmc.14.5.

36) Sheng S, Wang J, Wang L, Liu H, Li P, Liu M, Long C, Xie C, **Xie*** X, Su* W. Network pharmacology analyses of the antithrombotic pharmacological mechanism of Fufang Xueshuantong Capsule (复方血栓通等以指导临床组合用药)with experimental support using disseminated intravascular coagulation rats. *Journal of ethnopharmacology*. 2014;154(3):735-44.

37) Ouyang Q, Wang L, Mu Y, **Xie* X-Q**. Modeling skin sensitization potential of mechanistically hard-to-be-classified aniline and phenol compounds with quantum mechanistic properties. *BMC Pharmacology and Toxicology*. 2014;15:76 PMCID: PMC4298069 doi: 10.1186/2050-6511-15-76].

*FDA consortium publication

38) Liu H, Wang L, Su W, **Xie* X-Q**. Advances in recent patent and clinical trial drug development for Alzheimer's disease. *Pharmaceutical Patent Analyst*. 2014;3(4):429-47. doi: 10.4155/ppa.14.22.

39) Liu H, Wang L, Lv M, Pei R, Li P, Pei Z, Wang Y, Su W, **Xie* X-Q**. AlzPlatform: An Alzheimer's Disease Domain-Specific Chemogenomics Knowledgebase for Polypharmacology and Target Identification Research. *Journal of Chemical Information and Modeling*. 2014;54(4):1050-60. PMID:24597646 doi: 10.1021/ci500004h. (**Invited Journal Coverpage of the issue**).
(松柏白子仁 48 种天然成分靶点预测验证)

* This article was selected by Dr. Professor Kenneth M. Merz, Jr., Editor-in-Chief, Journal of Chemical Information and Modeling for the journal cover page. This is a first Alzheimer's disease knowledgebase reported with integrated chemical genomics information and built-in computing tools/algorithms to facilitate the Alzheimer's drug discovery and target identification as well as polypharmacology signaling pathway studies.
Coverpage caption: AlzPlatform (www.CBLigand.org/AD/) is an Alzheimer's Disease (AD) domain-specific chemogenomics knowledge base, featuring a large repertoire of AD drugs and small chemical molecules as well as related genes and protein targets. The comprehensive database and powerful computational algorithms and tools implemented have been developed and maintained by Xie's laboratory (www.CBLigand.org/XieLab) to facilitate target identification, drug repurposing, and system polypharmacology analyses in a chemogenomics scale for new anti-AD drug discoveries.

40) Feng Z, Alqarni MH, Yang P, Tong Q, Chowdhury A, Wang L, **Xie* X-Q**. Modeling, Molecular Dynamics Simulation, and Mutation Validation for Structure of Cannabinoid Receptor 2 （大麻受体 CB2）Based on Known Crystal Structures of GPCRs. *Journal of Chemical Information and Modeling*. 2014;54(9):2483-99. doi: 10.1021/ci5002718.

*Xie is the first author published first 3D structure model of Cannabinoid Receptor CB2 in 2003 (Xie et al Proteins). With such predicted 3D CB2 model, his group has *in silico* screened and published/patented several new CB2 ligands with therapeutic potential. This new 3D structure model of CB2 is further improvement and a new discovery of a potential allosteric binding site for the G-protein coupled CB2 receptor (GPCR), a very important drug target but no experimental structure.

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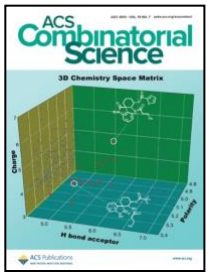

* This peer-reviewed research article was invited by Dr. M.G. Finn, ACS Editor-in-Chief as a cover page issue of *ACS Comb Sci Journal*. Xie group applied his developed powerful 3D chemistry-matrix compound library profiling algorithm tool to evaluate and visualize structural and stereochemical diversity of compound library. The program has been extensively used by chemists (including Dr. MG Laporte and PE Floreancig groups here as an example) in combinatorial chemistry to design structurally-divesed drug chemical molecules for diversity oriented synthesis

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128) Moring J, Duclos RI, Jr., Zhang JH, Herbette LG, Xie X, Makriyannis A. Single crystal X-ray structures of the two 4-heptadecyl derivatives of (1R,5S)-3,6,8-trioxabicyclo[3.2.1]octane. *Chemistry and physics of lipids*. 1995;77(1):99-112.

129) Xie **X-Q**, Yang D-P, Melvin LS, Makriyannis A. Conformational Analysis of the Prototype Nonclassical Cannabinoid CP-47,497, Using 2D NMR and Computer Molecular Modeling. *Journal of Medicinal Chemistry*. 1994;37(10):1418-26. doi: 10.1021/jm00036a006.

130) Xie **XQ**. Conformational studies of non-classical cannabinoids: an analysis using high resolution 2D NMR and computer molecular modeling 1993.

131) Dora G, Xie **XQ**, Edwards JM. Two novel phenalenones from Dilatris viscosa. *Journal of Natural Products*. 1993;56(12):2029-33. doi: 10.1021/np50102a001.

Books and Book Chapters:

1) **Xie, X.-Q**. (book chapter) 2007 “Molecular Modeling and In-silico Drug Design” in Foye’s Principles of Medicinal Chemistry (editors: D.A. Williams and T. L. Lemke), 6th edition, p.p.54-84, Lippincott Williams & Wilkins(ISBN 978-0-7817-6879-5), Baltimore, MD 21201.

2) Myint KZ, **Xie XQ***. "Ligand biological activity predictions using fingerprint-based artificial neural networks (FANN-QSAR)". ***Methods Mol Biol***. 2015;1260:149-64. PMID: 25502380. doi: 10.1007/978-1-4939-2239-0_9.

3) **Xie, X.Q***., Chowdhury, A., " Advances in methods to characterize ligand-induced ionic lock and rotamer toggle molecular switch in G protein-coupled receptors". ***Methods Enzymol*** 2013, **520,** 153-174. PMID: 23332699; NIHMSID: 562667. doi: 10.1016/B978-0-12-391861-1.00007-1.

c. Xie for *Invited Lectures/Chair and National/International Meetings*

1) (Invited speaker) Xie, XQ, 2017 Dec 8 "Chemogenomics Systems Pharmacology Approach for TBI and AD Research" Department of Defense (DOD) Research Progress Report. US Army Contract #: W81XWH-16-1-0490. Fort Detrick, Frederick, Maryland 21702-5000. http://www.detrick.army.mil/services/visitors.cfm

2) (Invited chair) **Xie, XQ,** 2017 Nov30-Dec 1, 2017 "China (Beijing) International Technology Transfer Convention (ITTC) 2017" Special Topics Session: China and the US Technology Development: Difference and Uniqueness

3) (Invited Speaker) **Xie, XQ**, 2017 Dec 2, 2017 Sino-American International Biomedical Development Forum and Taizhou "500 elite plan" competition: Anti-Multiple myeloma New Drug Research and Development. Class A award, Taizhou, Zhejiang Province, China

4) **Xie, XQ , Chair, leading Organizer and speaker** of 2017 Annual Meeting of NIH Center of Excellence for CDAR and External Advisory Board member meeting, August 15, 2017 Pittsburgh, PA.

5) (Invited speaker) **Xie, XQ,** 2017 Sept 28. "First-in-Class Sequestosome-1/p62 target specific Novel Anti-Multiple Myeloma (MM) Drug" 2017 Sino-American Pharmaceutical Professional Association (SAPA) Venture Summit Roadshow Competition 2nd Prize Award

6) (Invited speaker) Xie, XQ, 2017 Aug 9-12 "Chemogenomics Knowledgebase System Pharmacology (KSP) for Computational Drug Abuse and Neurodisorder Research" Chemistry & Pharmacology of Drug Abuse Conference, Northeastern University, Boston, Massachusetts

7) (Invited speaker) Xie, XQ, 2017 Aug 31 : An Integrated Platform of "big data to knowledge": Diseases-Specific Chemogenomics Knowledgebases and TargetHunter© for Precision System Pharmacology Drug Design and Discovery. Tasly R&D Institute, Tianjin, China

8) (Invited speaker) Xie, XQ, 2017 Aug 26 "VR-AR-MR Innovation for Medicine and Pharmacy. Cloud Mixed/Augmented Reality(s) Innovation (C-MARs). 2017 Joint US Silicon Valley-China JiaShan Global Innovation AI Competition 2nd Prize Award

9) (Invited speaker) Xie, XQ, 2017 May 18 "Novel anti-multiple myeloma drug for FDA IND-enabling studies" 2017 Innovation and Development Summit of Pujiang Pharmaceuticals Shanghai China

10) (Invited speaker) **Xie, XQ,** 2017 Feb 6. "GPU-accelerated Computational Chemogenomics Knowledgebase-guided Drug Target Identification and System Pharmacology for Translational Research". NIH Center for Substance Abuse Research, Temple University, Lewis Katz School of Medicine, Philadelphia, PA

11) (Invited speaker) **Xie, XQ,** 2017 Feb 2nd, "An Integrated Platform of "big data to knowledge" Diseases-Specific Chemogenomics Knowledgebases and TargetHunter©" Merck Research Laboratories, 2000 Galloping Hill Road, Kenilworth, NJ 07033

12) (Invited speaker) **Xie, XQ,** 2016, Oct 24, "Precision Medicine via Chemogenomics Knowledgebase TargetHunter© --- Alzheimer's disease drug research from bench top to beside", Biogen Inc. Building 6 (115 Broadway, Cambridge MA 02142

13) (Invited speaker) **Xie, XQ,** 2016 Feb 2, "Precision Pharmacology Benchtop to Bedside: Thinking inside Precision Medicine via Diseases-Specific Chemogenomics Knowledgebases and TargetHunter©" College of Pharmacy, University of Georgia, Atlanta, Georgia

14) **Xie, XQ , Chair, leading Organizer and speaker** of 2016 Innovation Research and Annual Meeting of NIH Center of Excellence for CDAR and External Advisory Board member meeting, Pittsburgh, PA.

15) (Invited speaker) **Xie, XQ,** 2016 May 27, "Clinical System Pharmacology by Chemogenomics Knowledgebase", 2016 Sino-America Forum of Clinical Pharmacy at Fudan University, China

16) (Invited speaker) **Xie, XQ,** 2016 June 4 "Benchtop to Bedside" Precision System Pharmacology by Chemogenomics Knowledgebases and TargetHunter©" Tasly R&D Institute, China

17) (Invited speaker) **Xie, XQ,** 2016 June 3, "Precision System Pharmacology. A Case Study "Benchtop to Bedside" of Alzheimer's Disease (AD) via Chemogenomics Knowledgebases and TargetHunter©", Medicinal Chemistry Biology Key Laboratory, Nankai University, China

18) (Invited speaker) **Xie, XQ,** 2016 June 13, "Stem Cells-specific Chemogenomics Knowledgebase and Discovery of First INK4C Chemical Modulator for Hematopoietic Stem Cell Expansion", Seoul National University, South Korea.

19) (Invited speaker) **Xie, XQ,** 2016 June 16, "Precision Pharmacology. Thinking inside Precision Medicine via Diseases-Specific Chemogenomics Knowledgebases and TargetHunter©". 2016 Bit's 14th Annual Congress of International Drug Discovery Science and Technology, June 16-18, Gyeonggi, South Korea.

20) (Invited speaker) **Xie, XQ,** 2016 June 20, "GPU-accelerated Cloud Computing Chemogenomics Knowledgebases and TargetHunter© for Precision System Pharmacology and Drug Discovery" Guangzhou Branch of Chinese Academy of Sciences, Guangdong, China

21) Invited Speaker, 2016 Jan 20 "Short-Term and Long-Term Strategic Plans and Execution", College of Pharmacy, University of Hawaii, Hilo, Hawaii.

22) Invited speaker, 2016, January 27, "Precision System Pharmacology for Multiple Myeloma and Osteoporosis: Thinking Inside Precision Medicine via Diseases-Specific Chemogenomics Knowledgebases and TargetHunter©", Pittsburgh Center for Bone & Mineral Research Seminar Series, University of Pittsburgh.

23) Speaker and organizing committee chair, symposium "Pharmaceutical Sciences in the Era of Big Data" 2015 AAPS Annual meeting, Orlando, Florida, USA. October 21-26, 2015

24) Speaker/Chair, "Computational Chemogenomics Knowledgebase for Drug Abuse Research", National Center for Computational Drug Abuse Research (CDAR), May 14, 2015

25) Invited Speaker 2015 April 10, "Diseases-Specific Chemogenomics Knowledgebases and TargetHunter© for System Pharmacology and Alzheimer's Disease Drug Discovery Research", FDA - Center for Devices and Radiological Health, Office of Science and Engineering Laboratories , Division of Biology, Chemistry, and Materials Science, Silver Spring, MD, USA

26) Invited Speaker 2015 March 12, "Diseases-Specific Chemogenomics Knowledgebases and TargetHunter© for System Pharmacology and Alzheimer's Disease Drug Discovery Research" Alzheimer's Disease Clinical Research Center, School of Medicine, University of Pittsburgh, PA

27) Invited Speaker 2015 Feb "Diseases-Specific Chemogenomics Knowledgebases and Drug TargetHunter© Center for Drug Discovery (CDD), School of Pharmacy, Northeastern University, Boston, MA USA

28) Invited Speaker 2015 Jan 30, "Diseases-Specific Chemogenomics Knowledgebases and TargetHunter© for Quantitative System Pharmacology" Department of Informatics, University of Pittsburgh, PA

29) Invited Speaker 2014 "Cloud Computing and Diseases-Specific Chemogenomics Knowledgebase for System Pharmacology Drug Discovery and Personalized Medicine" at New Frontiers in Therapeutic Agents – Successes in Drugging the Undruggable Conference, jointly sponsored by the John S. Dunn Gulf Coast Consortium for Chemical Genomics (GCCCG) and the Texas Screening Alliance for Cancer Therapeutics (TxSACT). April 16-17, 2014, The University of Texas MD Anderson Cancer Center, Houston, Texas. USA.

30) Invigted Speaker 2014 "Manipulation of Hematopoietic Stem Cell Expansion by INK4C Chemical Inhibitors" December 18, 2014, Stem Cell Research Center, University of Pittsburgh, Pittsburgh USA

31) In vited Speaker 2014 "Cloud Computing Target Hunter and Disease-Specific Chemogenomics Knowledgebase for System Pharmacology Drug Discovery and Personalized Medicine". June 23, 2014 University of Florida, Gainseville, Florida, USA

32) Invited 2013 "Cloud Computing and Diseases Domain-Specific Chemogenomics Knowledgebases for Systems Pharmacotherapy and Personalized Medicine." Workshop on Quantitative Systems Pharmacology in Personalized Medicine. Nov. 2013, Pittsburgh, USA.

33) Invited seminar speaker, April 24, 2012, "Computational Chemical Genomics Screening Center" Department of Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

34) Invited speaker, March, 28, 2012, "Computational Chemical Genomics Screening Center", Department of Developmental Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

35) Invited speaker, December 19, 2011 "GPCR Chemical Genomics for Drug Discovery", Shanghai JiaoTong University, College of Pharmacy, Shanghai, China

36) Invited speaker, December 28, 2011 "Computational GPCR Chemical Genomics for Drug Discovery", Sun-Yat Sen University, College of Life Sciences, Guangzhou, China

37) Invited speaker, July 28, 2011 "GPCR Chemical Genomics for Drug Discovery", Shanghai NanKai University, College of Pharmacy, Tianjin, China

38) Invited speaker, June, 10, 2012, "Cloud computing and High Throughput Experimental Chemical Genomics Screening Approaches for Lead Discovery", Jinan University, GuangZhou, China

39) Invited speaker, June, 20, 2012, "Cloud computing and High Throughput Experimental Chemical Genomics Screening Approaches for Natural Product Target Identification and Lead Discovery", Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, China

40) Invited speaker, June, 23, 2012, "Computational Chemical Genomics Screening Approaches for Natural Product Target Identification and Lead Discovery", XiShuanBanNan Tropical Botanic Garden, Chinese Academy of Sciences, XiShuanBanNan, China

41) Invited speaker: March, 2010 "GPCR Chemical Genomics for Drug Discovery". Albany College of Pharmacy, Albany, USA

42) Invited speaker: Sept., 2009 “Structurally-Diverse Chemical Library Design and In Silico Screening”, Dept of Chemistry, Duke University, USA

43) Invited speaker: Feb. 2008 “In Silico and In Vitro Chemical Genomics Approaches” P50 Center grant research project meeting, Dept of Chemistry, University of Pittsburgh, USA

44) Invited Speaker: Nov 2007 “Chemical Genomics for GPCR Drug Discovery” Dept of Structural Biology, School of Medicine, University of Pittsburgh, USA

45) Session chair, organizer and invited speaker: Oct. 2006, “Transforming Marijuana Receptors to a Gold Target: GPCR Membrane Protein NMR.” 62nd Southwest Regional Meeting of the *American Chemical Society*, Houston, Texas, USA

46) invited speaker: Nov. 2005 “Integrated In-Silico and In-Vitro HTS for GPCRs” *Neuroscience Symposium*, Cornell Medical-the Methodists Hospital-UH Initiative, Houston, Texas, USA

47) invited speaker: Nov.. 2005 “A Combined In-Silico and In-Vitro Screening Approach for CB2 ImmunoTherapy Drug Discovery.” *Infectious Diseases Workshop.* The Methodist Hospital Research Institute - University of Houston, The Methodist Hospital, Houston, Texas, USA.

48) invited speaker: April, 2005, “Membrane GPCR Proteins- the Wild Wild West of Structural Biology”, Dept of Biochemistry & Biology, University of Houston, Texas, USA.

49) invited speaker : April, 2005, “Nanostructured GPCR Assembly towards In-silico Design and Virtual Screening”, NIH-NCRR RCMI Program 20th Annual Meeting, Houston, Texas, USA.

50) invited speaker: November, 2004, “The Blockbuster Drug Targets - Seven Transmembrane GPCRs”, Membrane Biology Symposium 2004 Houston, Houston, Texas, USA.

51) invited speaker: October, 2004, Gulf Coast Consortium – Keck Seminar Series, Rice University (Invited speaker) “A Weed Receptor or A Gold Drug Target”, Houston, Texas, USA.

52) invited speaker: “GPCR Structural Proteomics. Receptor-based in-silico virtual Screening” College of Natural Sciences, University of Houston and Lexicon Pharmaceutical Company, Houston. 9/12/2004 (应邀出席休士顿大学和 LEXICON 公司联合会议) , USA.

53) invited speaker January, 2003(contractor for data report), Boston Scientific Corporation “High-resolution and Solid-state CP/MAS NMR Investigation of Nano Taxol-Polymer Control Release Formulation” , USA.

54) invited speaker: October, 2002 University of Iowa, College of Pharmacy, Iowa City “A Promising Platform for GPCR Drug Discovery” , USA.

55) invited speaker: Dec., 2002 University of Minnesota, College of Pharmacy, Minneapolis “Recombinant Isotope Protein Engineering NMR Study of G-Protein Coupled CB2 Receptor for Drug Discovery” , USA.

56) 管理企业分析演讲：Case Analysis and Presentation: M&A Pfizer vs. Warner-Lambert and Galxowellcome vs. SmithKline Beecham., USA

Invited Speaker – Xiang-Qun Xie (National and International)

57) XQ Xie, an Invited speaker by Merck Sharp & Dohme Corp 2017 Feb 2, "Chemogenomics-based Target Identification and System Pharmacology for Translational Research. A case study of novel anti-multiple myeloma (MM) drug discovery." Merck Research Laboratories, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., 33 Avenue Louis Pasteur, Boston, MA 02115-5727.

58) XQ Xie, an invited speaker by Biogen Company 2016 Oct 24, "Precision Medicine via Chemogenomics Knowledgebase TargetHunter© -- Alzheimer's disease drug research from bench top to beside." Chemistry and Molecular Therapeutics, Biogen Company, 115 Broadway, Cambridge, MA 02142

59) Invited speaker and session chair, "TargetHunter© and Diseases-Specific Chemogenomics Knowledgebases for Multiple Myeloma Drug Discovery" in 2014 International Symposium on Clinical and translational Medicine: Sub-session on "The Cancer prevention and control". Sino-American Symposium in China with co-organizers from the Chinese Academy of Engineering (CAE), Chinese Academy of Sciences(CAS) and the U.S. National Institute of Health Clinical Center. May 28-31, 2014, Shanghai, China.

60) Invited speaker, "Cloud Computing TargetHunter© and Diseases-Specific Chemogenomics Knowledgebases for Multiple Myeloma Drug Discovery" Institute of Materia Medica, Chinese Academy of Sciences(CAS), June 9, 2014, Beijing, China

61) Invited Keynote Speaker and Organizing Committee Member/Session Chair, Oct 15, 2013, "Cloud Computing Chemogenomics Knowledgebase Platform for Drug Discovery" in 2nd International Conference on Medicinal Chemistry & Computer Aided Drug Designing", Las Vegas, USA. www.omicsgroup.com/conferences/medicinal-chemistry-computer-aided-drug-designing-2013/committee.php

62) Invited speaker, Nov 2012, " Novel Small Chemical Inhibitors Targeting p18INK4C Protein for Hematopoietic Stem Cell Expansion", 3rd International Forum on Stem Cells 国际干细胞论坛, Tianjin, China.

63) Invited speaker, May 9, 2013 "Target Hunter for Natural Product Research", West China School of Pharmacy, Sichuan University, Chengdu, China

64) Speaker, July, 2012, "Cannabinoid receptor CB2. a new drug target for multiple myeloma intervention" International Cannabinoid Research Society Symposium, Freiburg, Germany and "Cloud computing webserver for cannabinoid research" (www.CBLigand.org/CBID), Freiburg, Germany

65) Myint, K-Z., Wang, L. and Xie, X-Q. Fingerprint-based Artificial Neural Networks Approach to predict GPCR Cannabinoid Ligand Binding Activities. Podium Presentation in Ligand-based Drug Discovery Symposium, Division of Computers in Chemistry, 243rd ACS National Meeting, San Diego, CA (2012).

66) June, 2004(speaker), International Cannabis Research Society (ICRS) Meeting, "CB2 receptor: protein NMR from building blocks to 3D structure" Italy, Peastum

67) Chair/Speaker, February 14, 2012, *4th International Conference on Drug Discovery & Therapy*: "Novel Target and Novel Chemical Agents Potential for Multiple Myeloma Treatment" Dubai, UAE.

68) Invited Speaker, Jan 5, 2012, "GPCR Computational Chemical Genomics for Drug Discovery". Shanghai JiaoTong University, College of Pharmacy, Shanghai, China.

69) Invited Speaker, Dec 26, 2011, "Computational Chemical Genomics Screening Center". Sun Yat-Sen University, School of Life Sciences, Guangzhou, China.

70) Chair/Speaker, May 2010, International Medicinal Chemistry Symposium, Virtual Screening and Combinatorial Chemistry Library Session: "3D Pharmacophore Database Searches of CB2 Ligands with Therapeutic Potential, Beijing, China

71) Speaker, June, 2009, International Cannabinoid Research Society Meeting, "Discovery of New CB2 Ligands with Novel Chemical Scaffolds", Chicago, USA.

72) Invited speaker: August, 2009, Institute of Biomedical Sciences and School of Life Sciences, East China Normal University, "GPCR Chemical Genomics Drug Design" Shanghai, China .

73) Invited speaker: August, 2009 College of Pharmacy, Second Military Medical University, "Computational Chemical Genomics for GPCR Drug Discovery", Shanghai P. R. China.

74) Session Chair and invited speaker: October 18-21, 2008 "In silico and in vitro chemical genomics screenings for GPCR Drug Discovery" International Drug Discovery and Technology Symposium 2008, Beijing China.

75) invited speaker : September, 2005, "Post Receptor Events in Cell Signaling and Disease" Workshop, University of Dundee, United Kingdom, sponsored by Texas/United Kingdom Collaborative Research Initiative.

76) invited speaker: July, 2005, 8th International Peptide Symposium "GPCR Structural Proteomics: Recombinant protein engineering/isotope editing NMR for membrane protein." China, Kunming.

77) June, 2004(speaker), International Cannabis Research Society (ICRS) Meeting, "CB2 receptor: protein NMR from building blocks to 3D structure" Italy, Peastum.

78) June, 1999(speaker), International Cannabis Research Society (ICRS), "Web-depolyed Interactive Database for Cannabinoid Ligands" Acapulco, Mexico.

79) February, 1999(speaker), 40th Experimental Nuclear Magnetic Resonance Conference (ENC), "REDOR NMR Determination of Intermolecular Distance of Endogenous Cannabinoid Ligand Anandamide in Membrane" Orlando, Florida.

80) invited speaker: July, 1999, International Academic Exchange program – China International Brigdge: "G-protein coupled Cannabinoid Receptors and Novel Drug Design" Zhejiang University, College of Pharmacy (Hongzhou); Zhejiang Academy of Medical Sciences (Hongzhou); Wuxi University of Light Industry (Jiangsu); and Second Military Medical University (invited guest speaker) P. R. China.

81) invited speaker: December, 1998, International Academic Exchange program **"**Integrated NMR/computer Modeling Approach for Rational Drug Design" Shanghai Institute of Materia Medica (Chinese Academy Sciences); East China Normal University (Shanghai), Fudan University (Shanghai); Institute of Materia Medica, Chinese Academy of Medical Sciences (Beijing); National Center for Biomedical Analysis (Beijing); and Second Military Medical University (invited guest speaker) P. R. China.

d. National/International meeting Abstracts Poster Presentations(selected)

82) **Zhang,Y**, Feng ZW, Yang,P and **Xie, X-Q**.* Novel agonists for hematopoietic stem cell expansion targeting protein-protein interface of p18(INK4C) and CDK6. Poster in 2015 Annual Meeting NIH National Center of Excellence for Computational Drug Abuse Research (CDAR), Pittsburgh, PA (2015).

83) **Li PL**, Wang L, Li, P, Su W, **Xie XQ***. Chronic Obstructive Pulmonary Disease Specific Chemogenomics Knowledgebase Construction and Application to the Polypharmacology Analysis of Naringin. Poster in 2015 Annual Meeting NIDA-Funded National Center of Excellence for Computational Drug Abuse Research(CDAR), Pittsburgh, PA(2015).

84) **Ma SF**, Yang XL, Feng ZW, Yang P, Wang LR, **Xie XQ ***. "CRC Platform: A Colorectal Cancer Domain-specific Chemogenomics Knowledgebase for Polypharmacology and Target Identification Research" Poster in Regional American Association of Pharmaceutical Scientists (AAPS) Meeting & Research Forum, Pittsburgh, PA (2014).

85) **Ma SF,** Feng ZW, Hu GX, **Xie XQ ***. "Structural Insight into the Allosteric Binding Site and Activation Mechanism of Class C G-Protein Coupled Receptors: Metabotropic Glutamate Receptor Family." Center of Drug Abuse Research (CDAR) annual meeting poster (2015)

86) **Hu, Z**H., Du, S., Yang, P., Hye-Yeong Kim, HY., Tong, Q., Wang, XL., Edwards, B.W., Calero, G.V.*, and **Xie, X-Q.*** Structural Studies on p18INK4c in Complex with Small-molecular Inhibitors using X-ray Crystallography. Poster in Research Retreat of School of Pharmacy University of Pittsburgh, Wheeling, WV (2015).

87) **Xu, X**M.; Hu, G.; Feng, Z.; **Xie*, X.-Q**."Computational Chemogenomics Systems Pharmacology for Hallucinogen Target Identification. Salvinorin A as a Case Study." Poster in NIH CDAR Center Annual Meeting, Pittsburgh, PA (2015).

88) **Hu, GX**, Feng, ZW, Ma, SF, and **Xie, XQ** *. "Advances in the Computational Development of Allosteric Modulators and Bitopic Ligands for G Protein-Coupled Receptors." Poster in 2015 Annual Meeting of the NIDA-funded National Center of Excellence for Computational Drug Abuse Research, Pittsburgh, PA (2015)

89) **Feng, Z.;** Pearce, L. V.; Xu, X.; Yang, X.; Yang, P.; Blumberg, P. M.; **Xie*, X.-Q.** Structural Insight into Tetrameric hTRPV1 from Homology Modeling, Molecular Docking, Molecular Dynamics Simulation, Virtual Screening and Bioassay Validations. 59th Annual Meeting, Feb 7-11,2015 (Baltimore, Maryland).

90) **Feng, Z.;** Alqarni, M. H.; Yang, P.; Tong, Q.; Chowdhury, A.; Wang, L.; **Xie*, X.-Q.** 3D Structural Model of Cannabinoid Receptor 2 Based on Recently Published Crystal Structures of GPCRs. 6th Annual Pittsburgh Student Chapters' Research Symposium. AAPS, Oct 17th, 2014.

91) **Feng, Z.;** Pearce, L. V.; Xu, X.; Yang, X.; Yang, P.; Blumberg, P. M.; **Xie*, X.-Q.** Computational Approach to Discovery of Novel Antagonists of Transient Receptor Potential Vanilloid Type 1(Poster). NIH National Center of Excellence for Computational Drug Abuse Research P30 EAB Annual Meeting, Pittsburgh, 2015 May 14.

92) **Yang P.**, Teramachi J., Wang L., Myint K., Beumer J., Eiseman J., Roodman D., Kurihara N., **Xie* X-Q.** Discovery and Chemical Modification of the First p62-ZZ Small molecule Inhibitor with Anti-tumor Potential. Poster in Annual Retreat of School of Pharmacy. Pittsburgh, USA, May, 2015.

93) **Yang P.**, Wang L., Almehizia A., Tong Q., Alqarni M., Wang L., and **Xie* X-Q.** Discovery and Chemical Modification of Novel Triaryl Sulfonamides as Selective Cannabinoid Receptor 2 Inverse Agonists. Poster in 2015 EAB Annual Meeting of the NIH National Center of Excellence for Computational Drug Abuse Research (CDAR). Pittsburgh, USA, May, 14, 2015.

94) Yang P., Zhang P., Zhang Y., Wang L., Tong, Q., Cheng T., Gao Y., and **Xie X.Q***. Novel p18INK4C small molecule inhibitors for hematopoietic stem cell expansion. ACS 2014 Central Regional Meeting. Oct, 2014, Pittsburgh, USA.

95) Yang P., Wang L., Almehizia A., Tong Q., Alqarni M., Wang L., and **Xie X-Q***. Discovery, Optimization, and Biological Evaluation of Novel Cannabinoid Receptor 2 (CB2) Ligands for Osteoporosis Treatment. 2014 AAPS Annual Meeting and Exposition. Nov, 2014, San Diego, USA.

96) Yang P., Teramachi J., Feng R., Wang L., Beumer J., Eiseman J., Roodman D., Kurihara N., **Xie X-Q*.** A Novel Chemical Inhibitor Targeting Sequestosome-1/p62 Suppresses Multiple Myeloma Cell Growth and Osteoclast Formation. 2014 AAPS Annual Meeting and Exposition. Nov, 2014, San Diego, USA.

97) **Alqarni MH**, Sun B, Tong Q , KobilkaB and **Xie, X-Q**, Proposed Structural and Functional Studies of Human Cannabinoid Receptor 2 Expressed and Purified from Insect Cells.Poster in NIDA-

Funded National Center of Excellence for Computational Drug Abuse Research (CDAR), May 14, 2015 Pittsburgh, PA

98) Almehizia A., Yang P, Zhiewi F, Tong Q, and Xie X-Q. (Poster) Design, Synthesis and biological evaluation of 4-(aminomethyl)-N, N-diethylaniline Derivatives as Selective Cannabinoid of Receptor 2 Ligands with Potential Anti-Multiple Myeloma Activity. GPCR: Structure, Function and Drug Discovery Conference, Boston May 2014.

99) Alqarni, MH , Feng Z, Tong Q, Wang L, Yang P, and **Xie XQ***. In Silico Prediction and Site-directed Mutagenesis Study of Binding Pocket Residues of Cannabinoid Subtype 2 (CB2) Receptor; Protein Discovery Summit 2014, October 23-24, 2014 in Boston, MA .

100) Ma SF, Yang XL, Feng ZW, Yang P, Wang L, **Xie XQ *.** "CRC Platform: A Colorectal Cancer Domain-specific Chemogenomics Knowledgebase for Polypharmacology and Target Identification Research" AAPS Regional Meeting, Pittsburgh, 2014

101) Almehizia A., Yang P, Zhiewi F, Tong Q, and **Xie X-Q***. Design, Synthesis and biological evaluation of 4-(aminomethyl)-N, N-diethylaniline Derivatives as Selective Cannabinoid of Receptor 2 Ligands with Potential Anti-Multiple Myeloma Activity. GPCR: Structure, Function and Drug Discovery Conference, Boston May 2014.

102) Ma SF, Yang XL, Feng ZW, Yang P, Wang L, Xie XQ *. "CRC Platform: A Colorectal Cancer Domain-specific Chemogenomics Knowledgebase for Polypharmacology and Target Identification Research"

103) Michelle Rae, Mikhaila Rice, Brian Kocak, Sage Smith, Thann Troung, Bhupinder Singh Shifan Ma, Xiaole Yang, Lirong Wang, and Xiang-Qun (Sean) Xie , "CK4CRC: A Domain Specific Chemogenomics Knowledgebase for Colorectal Cancer Research" Poster for Symposium of First Experience in Research, University of Pittsburgh,April,2014

104) Haibin Liu, Lirong Wang, Weiwei su, Xiang-Qun Xie, *et al*, ALzPlatform: a one-stop cloud computing server for Alzheimer's drug and targets research.(Poster, P50, 美国匹兹堡科学年会 Science, 2013)

105) Haibin Liu, Lirong Wang, Qin OuYang,Weiwei Su, Xiang-Qun Xie. Alzheimer's disease domain specific chemogenomics knowledgebase and polypharmacological network analysis for natural product research. (Poster, P31, the 5th Annual AAPS Pittsburgh Chapters Research Symposium. 2013, Pittsburgh, USA).

106) Haibin Liu, Lirong Wang, Xiang-Qun Xie. Cloud Computing Chemogenomics Knowledgebases and Cheminformatics Tools for PolyPharamcology Networks.(Poster, 18th Annual International Conference on Research in Computational Molecular Biology, 2014, Pittsburgh, USA)

107) Xiang-Qun Xie, Lirong Wang, Haibin Liu, Qin Ouyang, Zhiwei Feng. Cloud Computing and Diseases Domain-Specific Chemogenomics Knowledgebases for Systems Pharmacotherapy and Personalized Medicine. (invited Poster, Workshop on Quantitative Systems Pharmacology in Personalized Medicine. Nov. 2013, Pittsburgh, USA).

108) Haibin Liu, Lirong Wang, Qin OuYang,Weiwei Su, Xiang-Qun Xie*. Alzheimer's disease domain specific chemogenomics knowledgebase and polypharmacological network analysis for natural product research. (Poster, P31), 5th Annual AAPS Pittsburgh Chapters Research Symposium. 2013, Pittsburgh, USA).

109) Alqarni, M., Myint,K-Z., Tong, Q. , Yang, P., Bartlow, P. , Wang, L. , Feng, F. and Xie, X-Q. Important Binding Residues of CB2 Receptor Determined by In Silico Modeling and Site-Directed Mutagenesis. Poster in Regional American Association of Pharmaceutical Scientists (AAPS) Meeting & Research Forum, Morgantown, WV (2013).

110) Kyaw Z. Myint, Lirong Wang and Xiang-Qun Xie. “Artificial Neural Networks Approach to Predict GPCR Cannabinoid Ligand Binding Activities”. Oral Presentation in Ligand-based Drug Discovery Symposium, Division of Computers in Chemistry, 243rd ACS National Meeting, San Diego, CA (2012)

111) Lirong Wang, Chao Ma, Kyaw Zeyar Myint, Kay Brummond, Matthew LaPorte, Peter Wipf and Xiang-Qun Xie “Chemogenomics/Chemoinformatics Tools for Facilitating the Chemical Research in UPCMLD” Poster in 2012 CMLD Meeting on Frontiers in Accelerated Chemical Discovery, June 12, Bethesda, MD

112) Peng Yang, Kyaw-Zeyar Myint, Qin Tong, Abdulrahman A. Almehizia, Rentian Feng, Alqarni Mohammed Hamed, Lirong Wang, and Xiang-Qun Xie “Osteoclast inhibitor: discovery, synthesis and QSAR study of novel bi-amide derivatives as selective CB2 receptor inverse agonists” Poster in 2012 CMLD Meeting on Frontiers in Accelerated Chemical Discovery, June 12, Bethesda, MD

113) Lirong Wang, Matthew LaPorte, Peter Wipf and Xiang-Qun (Sean) Xie. “UPCMLD-ChemBioData: Data-Mining Compound Bioactivity from PubChem”. CMLD2011. Chicago(2011).

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115) Ma, Chao and Xie, Xiang-qun.* “Novel Ligand Classification Algorithm and Application on Modeling Functionality for 5HT1A GPCR Ligands” 18th Annual International Conference on Intelligent Systems for Molecular Biology, Boston, 7/2010 (Oral and poster presentation: software demonstration at Technology Track).

116) Myint, K-Z. Ma, C. Wang, L. and Xie, XQ.*: "The Fragment-Similarity-Based QSAR (FS-QSAR): A Novel 2D-QSAR approach for Ligand Biological Activity Predictions" 14th International Workshop on Quantitative Structure-Activity Relationships in Environmental and Health Sciences. Montreal, Canada, 2010.

117) **Xie, X.-Q.,** Chen, J. Z. And Zhang, Y. X. “Computational Chemical Genomics for GPCR CB2 Lead Discovery” Keystone Symposium Computer Aided Drug Design Symposium, March, 2008, USA

118) Sheng, W. Y. and **Xie, X.-Q.** * “Biosynthesis and NMR Analysis of a Transmembrane Helix-Bundle from G-Protein Coupled Receptor CB2.” 2007 IUPHAR, Beijing, China, 7/2006 (Student travel awarded) (Poster)

119) Sheng, W. Y. Zheng, H.A. and **Xie, X.-Q. *** “3D Triple Resonance NMR Characterization of CB2 Transmembrane Fragment” Thirty-Second Annual MALTO Medicinal Chemical-Pharmacognosy Meeting-in-Miniature Meeting, Oxford, MS, 5/2005 (awarded for the Best Poster Presentation).

120) Chen, J.Z., **Xie, X. Q.*** "NMR Structural Refinement of the Homology-Built 3d Cb2 Receptor Model" International Cannabis Research Society (ICRS) Meeting, 6/2005, Clearwater Beach, FL.

121) Zhang, Y; Zhao, J and **Xie, X.-Q.*** “A Practical Strategy for Solubilization and Fusion Partner Cleavage of a Recombinant GPCR Protein Fragment, $CB2_{180-275}$”. 10th Annual Structural Biology Symposium, Galveston, TX, 5/2005.

122) Zhao, J.; Zhang, Y.X.; Zheng, H.A. and **Xie, X.-Q.*** "13C/15N Isotope Labeled Human CB2 Receptor Fragment CB2271-326 for NMR Study" 10th Structural Biology Symposium, Galveston, 5/2005.

123) **X.-Q. Xie***; Zheng, H.A.; Zhao, J. and Chen, J.Z. "GPCR Structural Proteomics: Recombinant protein engineering/isotope editing NMR for membrane protein." International Peptide Symposium, China, Kunming, 7/2004. (100%).

124) **X.-Q. Xie***; Zhao, J.; Chen, J.Z. and Zheng, H.A. "CB2 receptor: protein NMR from building blocks to 3D structure" " International Cannabis Research Society (ICRS) Meeting, Italy Peastum, 6/2004. (100%).

125) Haian Zheng; Ju Zhao; Jianzhong Chen; and **Xiang-Qun Xie*,** "Protein Engineering and Isotope Aided NMR Study of Transmembrane Helical Domains from CB2 Receptor," *Membrane Protein: Structure and Mechanism*, Keystone Symposium, 2003 Taos, NW. (100%).

126) Ju Zhao, Feng Wang, Haian Zheng, Jianzhong Chen and **Xiang-Qun Xie*,** "IMS NMR Facility Web-Interfaced Reservation & Online Scheduling System," *Frontiers in Undergraduate Research Poster Exhibition*, 2003, University of Connecticut, Storrs, CT. (100%).

127) **Xie, X.-Q**.*; Zheng, H.-A.; Wang, S.; Chen, T. and Lin, C.-M. "Expression and Purification of Cannabinoid Receptor CB2 Fragment $CB2_{65-101}$" Cambridge Healthtech Institute's Fourth Annual *Protein Expression* Meeting, McLean, Virginia, April 5-6, 2001. (100%).

128) **Xie, X-Q.*,** and Chen, J. Z. "Computer Homology Model of the Marijuana-targeted GPCR: Cannabinoid Receptor CB2" GPCR Meeting, Boston, Oct. 30-31, 2000. (100%).

129) Chen, J. Z.; Yang, H. Q.; Makriyannis, A. and **Xie, X.-Q**.* "3D Structure Model of CB2 Cannabinoid Receptor" International Cannabis Research Society (ICRS) Meeting, Hunt Valley, MD, June21-24, 2000. (100%).

130) Chen, J. Z.; Han, X. W.; Lan, R.; Liu, Q.; Makriyannis, A. and **Xie, X.-Q**.* "3D QSAR Study of Cannabimimetic Diarylpyrazoles and Antagonistic Affinities for CB1 and CB2 Receptors by Using Comparative Molecular Field Analysis" International Cannabis Research Society (ICRS) Meeting, Hunt Valley, MD, June21-24, 2000. (95%).

131) **Xie, X.-Q**.*; Han, X. W.; Chen, J. Z.; Liu, Q. and Makriyannis, A. "Better Understanding of Conformational Properties of Anandamide" International Cannabis Research Society (ICRS) Meeting Acapulco, Mexico, June 18, 1999. (100%).

132) **Xie, X.-Q**.*; Chen, J. Z.; Hu, C.; Li, B.; and Makriyannis, A. "Web-depolyed Interactive Database for Cannabinoid Ligands (CBID)". ICRS Meeting. Acapulco, Mexico, June 18, 1999. (100%).

133) **Xie, X.-Q***.; Chen, J. Z.; Lin, S. Y.; Han, X. W.; and Makriyannis, A. **"**REDOR NMR Determination of Intermolecular Distance of Endogenous Cannabinoid Ligand Anandamide in Membrane". 40th Experimental Nuclear Magnetic Resonance Conference (ENC), Orlando, Florida, Feb. 28, 1999. (100%).

134) **Xie, X.-Q**., Makriyannis, A. ENC 95, Boston, MA "Studies of The Highly Selective Cannabinoid Receptor Ligand CP-55,940 in Membrane-Like Preparations Using 2D NMR Spectroscopy." 3/95.

135) **Xie, X.-Q**., Makriyannis, A. The 206th American Chemical Society National Meeting, Chicago, IL. "Stereochemical Requirements for Cannabinoid Activity in the Non-Classical Cannabinoids. A Comprehensive Combined 2D NMR and Molecular Modeling Approach" 8/93.

136) **Xie, X.-Q.**, Makriyannis, A. International Cannabis Research Society, L'esterel, Quebec, Canada, "Common Cannabimimetic Pharmacophoric Requirements between Amino-alkyl Indoles and Classical Cannabinoids" 7/94. .

137) **Xie, X.-Q**, Yang, D.P. and Makriyannis, A. The 23rd American Chemical Society, Boston, MA "Stereochemical Requirements for Cannabinoid Activity in the Non-Classical Cannabinoids. A Comprehensive Combined 2D NMR and Molecular Modeling Approach" 6/93.

138) Guo, Y. **Xie, X.-Q**., and Makriyannis, A. NERMCAP XVII (New England regional Medicinal Chemistry & Pharmacognosy Meeting), Boston, MA Oral presentation (Guo, Yan) "Synthesis, Conformational and Biological Properties of the 11-OH-1'1'-Dimethylheptyl-Hexahydrocannabinol Isomers" 5/93. (The poster received an award from SmithKline Beecham Pharmaceutical Company).

139) **Xie, X.-Q**., Makriyannis, A. NERMCAP XVII (New England regional Medicinal Chemistry & Pharmacognosy Meeting), Storrs, CT **"**Conformational Analysis of Non-Classical Cannabinoids Using 2D NMR and Computer Modeling" 5/92.

140) **Xie, X.-Q**., Makriyannis, A. Eastern Analytical Symposium, Somerset, NJ **"**Conformational Analysis of Non-Classical Cannabinoids Using 2D NMR and Computer Modeling" 7/92.

141) **Xie, X.-Q***., Makriyannis, A. NERMCAP XVI**,** Kingston, RI, **"**Conformational Analysis of Non-classical Cannabinoids CP-55,244 and CP-97,587 using 2D NMR Spectroscopy", 4/91.

142) The 4th Cyprus Conference on New Methods in Drug Research, Nicosia, Cyprus **(**Marvomoustakos, T.M.) "Interactions of Anesthetic Steroids with Model Membranes Using Solid State ^{2}H NMR", 5/89.

WEB PUBLICATIONS - Molecular information databases and Data-mining Tools:

Disease-specific Chemogenomics Knowledgebases:

1. Alzheimer's Disease, 2013 http://www.cbligand.org/AD 老年痴呆化学基因组学智能库）
2. Stem Cell , 2013, http://www.cbligand.org/stemcell （干细胞化学基因组学智能库）
3. Cardiovascular disease (CVD) : www.CBLigand.org/CVD心血管性化学基因组学智能库）
4. Drug abuse , 2013, http://www.cbligand.org/CDAR （滥用药化学基因组学智能）
5. Tussive, 2013 http://www.cbligand.org/tussive
6. Multiple Myeloma, 2013 http://www.cbligand.org/MM
7. Skin Allergen Predictor, 2013 http://www.cbligand.org/allergy
8. Immune Modulator of Small Molecule",2013 http://www.cbligand.org/IM
9. Thrombosis, 2013 http://www.cbligand.org/thrombosis
10. Prostate cancer , 2014 http://www.cbligand.org/PC
11. Colon cancer, 2014 http://www.cbligand.org/CRC
12. Diabetes, 2014, http://www.cbligand.org/DM
13. Osteoporosis,2014, http://www.cbligand.org/OP
14. Liver fibrosis, 2013, http://www.cbligand.org/liver_fibrosis
15. Parkinson Disease, 2013, http://www.cbligand.org/PD

Computing Tools and programs

16. www.CBLigand.org/CBID the largest cannabinoid ligand database in the world. Web-interfaced drug or chemical repository architecture.
17. www.CBLigand.org/gpu GPU-accelerated molecular property calculation
18. www.CBLigand.org/TargetHunter Off-target Predictor to help characterization of off-target activities of a drug molecule or new target identification。
19. www.CBLigand.org/LiCABEDS Novel machine learning algorithm for compound biological classification prediction. Ligand Classifier of Adaptively Boosting Ensemble Decision Stumps (LiCABEDS)。
20. www.CBLigand.org/5HT1A Web-interfaced GPCRs functionality predictor designed using machine learning SVM and KNN algorithms www.CBLigand.org/HTDocking High through put docking virtual screening for quick lead discovery.
21. www.CBLigand.org/gdb13: World largest online chemical database (1 billion)
22. www.CBLigand.org/UPCMLD: A chemical biology metabase for NIGM funded University of Pittsburgh UPCMLD, UPCMLD-ChemBioDB
23. www.CBLigand.org/FPR False Positive Remover. Help to identify the false positive hits from high throughput screen experiments.
24. www.CBligand.org/BBB BBB-permeability predictor to predict drug or chemical compound permeability to cross blood brain barrier

C. RESEARCH, SCHOLARSHIP AND OTHER CREATIVE ACTIVITIES

Summary of Key Research and Achievements

As an **Associate Dean** for Research Innovation and a **PI/Professor** of an integrated Medicinal Chemistry Biology Platform of CompuLab, BioLab and ChemLab (www.CBLigand.org/xielab) and a charter member of the **Science Advisory Board to the US FDA**, I focus my research on target identification system pharmacology for drug lead/chemical probe discovery and cell signaling mechanism studies, with over 150 publications and 10 invention discovery patents. The innovation discoveries were achieved by my extensive training and solid working experience in development and application of artificial intelligent (AI) know-how technologies of *in silico design* and virtual drug screening, medicinal chemistry synthesis, and biophysics studies, as well as *in vitro* and *in vivo* experimental validation approaches. As such, I received the ***2014 AAPS Award for Outstanding Research Achievements, 2017 US-China Global Competition Prize and 2017 SAPA Innovation Prize Award***. Furthermore, I have acquired expertise in chemical biology research for bone marrow, blood and immune-origin cancer diseases, including our discovery of cannabinoid CB2-targeted functional agonist, inverse agonist and neutral antagonist with therapeutic potential (5 patents, 6 ***JMC*** and 2 ***PNAS***) and TRPV1 ligands for neuropathic pains (patent and ***AAPS J*** 2016), a world-**first** p62-ZZ chemical inhibitor for multiple myeloma (patents and ***Leukemia*** 2015, ***Nature Comm*** 2017, *PNAS* 2018), a world-**first** INKC4C/p18-targeted chemical inhibitor for hematopoietic stem (HSC) cell expansion (patent, ***Nature Comm*** 2015 and ***Sci Rep*** 2015), and so on. As Founding Director of CCGS Center, I served as co-PI and core Director on two NIH-funded center grants (PCMLD P50 and UP-CDC NCI/SAIC) and served as co-PI on NIH PMLSC grant. Currently, I serve as Director/PI of the NIH-funded National Center of Excellence for CDAR (www.CDARCenter.org). Thus, my extensive research experience and expertise in medicinal chemistry drug design, *in silico* system pharmacology screening and *in vitro/in vivo* bioassay validation, as well as structural/functional biology, plus my EMBA training and administrative experience, have prepared me to fulfill my role on this grant in all aspects of the proposed work. (*Xie as a senior correspondent or co-correspondent author)

1. **"Lead discovery, chemistry optimization, and biological evaluation studies of novel biamide derivatives as cannabinoid CB2 receptor inverse agonists and osteoclast inhibitors**". ***J Med Chem*** 2012, **55**(22):9973-9987
2. "**Modeling, Molecular Dynamics Simulation and Mutation Validation for Structure of CB2 Based on Known Crystal Structures of GPCRs**", ***J. Chem. Inf. Model***. 2014, **54**(9), 2483–2499. PubMed ID: 25141027.
3. **Targeting cannabinoid receptor-2 (CB2) pathway by phenylacetylamide suppresses the proliferation of human myeloma cells through mitotic dysregulation and cytoskeleton disruption**. ***Mol Carcinog*** 2015: 54(12):1796-806. doi: 10.1002/mc.22251. PMID: 25640641
4. "**Blocking the ZZ Domain of Sequestosome1/p62 Suppresses Myeloma Cell Growth and Osteoclast Formation In Vitro and Induces Dramatic New Bone Formation in Myeloma-Bearing Bones In Vivo**" ***Leukemia*** (**Nature**) 2016;30(2):390-8. PMID:26286116.
5. **"p62/Sequestosome-1 is an N-recognin of the N-end rule pathway which modulates autophagosome biogenesis.** ***Nat Commun.*** 2017;8(1):102. PubMed PMID: 2018807953.
6. "**Small-molecule Inhibitors Targeting INK4 Protein p18INK4C Enhance ex vivo Expansion of Haematopoietic Stem Cells**", ***Nature Comm***, 2015 6:6328. PMID: 25692908.

Contribution to Science (over 100 publications and 10 patents)

1. Novel GPCR cannabinoid receptor CB2 ligands and bone diseases in vitro and in vivo studies.

Cannabinoid receptor **CB2** is a promising therapeutic target for the treatment of autoimmune, inflammation, and immune-origin diseases, particularly for osteoporosis (a bone morphogenetic protein auto-immune disorder), multiple myeloma (MM) (immune B plasma caused bone disease). Dr. Xie and his team have discovered novel **CB2** chemical agents with potential therapeutics for multiple myeloma and osteoporosis diseases via his years of developed research and how-know technologies. We have reported that high levels of expression of active CB2 were observed in human MM cell lines and primary CD138+ myeloma cells. Our discovered CB2 ligand, phenylacetylamide (PAM, or XIE95), inhibits MM growth through cell cycle modulation, mitotic death and cytoskeleton disruption. In particular, our studies show that CB2 gene silencing rescues PAM-induced inhibition of MM cell proliferation. It was reported that CB2 is expressed in osteoclast and osteoblast as well as their precursor cells. $CB2^{-/-}$ mice showed accelerated age-related trabecular bone loss and cortical

expansion. $CB2^{-/-}$ osteoclast number and trabecular osteoblast activity were increased. The role of CB2 pathway is important in MM-induced bone remodeling. We have designed and synthesized a series of selective CB2 inverse agonists with novel chemical scaffolds, and top compounds showed excellent CB2 binding affinity (**K_i < 10 nM, selectivity index > 100**) and effective anti-osteoporosis and anti-MM activities as well as good drug-like properties with minor toxicity.

1. **Four Patents**: **Xie XQ***, "**Ligands specific for cannabinoid receptor subtype 2**". PCT/US2008/012395; WO 2009/058377; US20110118214 A1. (2) "**Novel cannabinoid receptor 2 (CB2) inverse agonists and therapeutic potential for multiple myeloma and osteoporosis bone diseases**". USSN 61/576,041, 2012.
2. Yang P, Wang L, Feng R, Almehizia AA, Tong Q, Myint KZ, Ouyang Q, Alqarni MH, **Xie XQ***: (a) "**Novel triaryl sulfonamide derivatives as selective cannabinoid receptor 2 inverse agonists and osteoclast inhibitors: discovery, optimization, and biological evaluation**." ***J Med Chem*** 2013, **56**(5):2045-2058. (b) "Lead discovery, chemistry optimization, and biological evaluation studies of novel biamide derivatives as CB2 receptor inverse agonists and osteoclast inhibitors". ***J Med Chem*** 2012, **55**(22):9973-9987.
3. Feng R, Tong Q, Xie Z, Wang L, Lentzsch S, Roodman GD, **Xie XQ***: **Targeting cannabinoid receptor-2 pathway by phenylacetylamide suppresses the proliferation of human myeloma cells through mitotic dysregulation and cytoskeleton disruption**. ***Mol Carcinog*** 2015:PMID: 25640641.
4. Feng RT, Milcarek CA, **Xie XQ***: **Antagonism of cannabinoid receptor 2 pathway suppresses IL-6-induced immunoglobulin IgM secretion**. ***BMC Pharmacol Toxico*** 2014, **15**:30 PMID:24913620

2. First p62ZZ chemical inhibitor with therapeutic potentials

Xie's lab was the ***first*** to discover and develop p62ZZ chemical inhibitors with promising anti-multiple myeloma (MM) therapeutic index (*Nature Leukemia* 2016) in collaboration with Dr. D Roodman and YT Kwon. Emerging studies show that regulatory roles of p62 in protein-protein interactions and autophagy have recognized **p62 as a viable therapeutic target** for the treatment of cancer and **neurodegenerative diseases**. Our discoveredp62ZZ lead (**#3** or **XRK3**) exhibited notable p62 antagonistic effects and significantly reduced survival of human MM cells and inhibited osteoclastogenesis (Patent: Xie *et al*. PCT/US2012/049911). **The specificity was confirmed by $p62^{-/-}$ experiments**, showing that the effects of inhibitor XRK3 on MM cells and tumor necrosis factor (TNF)-α-induced osteoclast (OCL) formation were lost upon $p62^{-/-}$ gene deficiency. Our preliminary lead chemistry modification produced more potent p62 inhibitor analogs (e.g., **XIE1-10b**: IC_{50} 1.12, **XIE1-62a**: 0.63 μM) with improved drug-like properties ($t_{1/2}$ = 4.5 hrs, Bioavailability 43%). The ***in vivo*** MM xenograft murine model revealed significantly inhibited MM tumor growth (>75%) and increased mean survival time (53%) compared with the control group. We have demonstrated that: • NF-κB and p38 MAPK signaling are increased in primary bone marrow stromal cells from MM patients; • genetic silencing or deletion of p62 in patient- or mouse-derived stromal cells resulted in a marked reduction in the capacity of stromal cells to support the growth of MM cells and osteoclastogenesis; • the p62 ZZ-type zinc finger domain was identified to be the structural basis of p62 to support osteoclastogenesis and the growth of MM cells. • p62-ZZ domain specificity of **XRK3** is confirmed by co-IP pull down assay. The discovered p62Z chemical inhibitors will be valuable chemical probe for studies of cell signaling pathways associated with diseases such as multiple myeloma. Currently, Xie's lab is working on p62 protein expression/purification and X-ray co-crystallography, ^{3}H-radiometric binding and fluorescence assay development for screening of new p62 agonist and antagonist.

5. **Xie X-Q**, inventor; (University of Pittsburgh, USA). assignee. **Preparation of p62-ZZ chemical inhibitors**. Application: WO patent 2016-US36241; 2016200827. 2016 20160607. **"P62-zz chemical inhibitors as Antitumor agents**" Application: WO patent 2012-US49911 2013022919. 2013 20120808. "**One kind of drug-resistant multiple myeloma animal model and its construction method**", Application: CN *patent* 2015-10223834 104830776. 2015 20150505.
6. Cha-Molstad H, Yu Ji E, Kim Jung G, Hwang J, Ganipisetti S, Lee Kyung H, Kim Bo Y, Yu Ji E, Hong Jin T, Feng Z, Yang P, McGuire T, Wang N, Jang Jun M, Ciechanover A, Inhee MJ, Kwang PK, **Xie X-Q***, Kwon YT*, & Kim, BY*. **p62/SQSTM1/Sequestosome-1 is an N-recognin of the N-end rule pathway which modulates autophagosome biogenesis**. ***Nat Commun.*** 2017;8(1):102. PubMed PMID: 2018807953.
7. Teramachi J, Rebecca S, Yang P, Zhao W, Mohammad K, Guo JX, Anderson HL, Zhou D, Feng R, Myint KZ, Maertz N, Beumer JH, Eiseman, JL, Windle JL, **Xie X-Q*,** Roodman D*, Kurihara N*. "**Blocking the ZZ Domain of Sequestosome1/p62 Suppresses Myeloma Cell Growth and Osteoclast Formation In Vitro and Induces Dramatic New Bone Formation in Myeloma-Bearing Bones In Vivo**" ***Leukemia*** (Nature). 2016;30(2):390-8. doi: 10.1038/leu.2015.229. PMID: 2015:1599270 (*co-correspondents).
8. Cha-Molstad, H, Kim JG, Hwang, J, Kim BY, Lee SH, Sung KW., Shim SM, Ganipisetti, S, Ciechanover, A, Kwon YT, Kim JG, Kim BY, McGuire, T, **Xie, X-Q*,** Mook-Jung, I*, Ciechanover, A*, Kwon YT*, **Regulation of autophagic proteolysis by the N-recognin SQSTM1/p62 of the N-end rule pathway**. ***Autophagy***. 2018;14(2):359-61. doi: 10.1080/15548627.2017.1415190. PubMed PMID: 2018:224510.

9. Yoo YD; Mun SR; Ji CH; Sung KW; Kang KY; Heo AJ; Lee SH; AN JK, HWANG J, **Xie X-Q;** Ciechanover A; Kim BY and Kwon YT. **N-terminal arginylation generates a bimodal degron that modulates autophagic proteolysis.** ***PNAS*** March 5, 2018. 201719110; https://doi.org/10.1073/pnas.1719110115

3. GPU cloud computing TargetHunter machine-/deep-learning programs and diseases domain-specific chemogenomics knowledgebases for target identification system pharmacology drug discovery

Xie's lab is known for its pioneering research for the development of diseases domain-specific chemogenomics knowledgebase database, an integrated artificial intellenget (AI) platform of target identification, system pharmacology and translational research. These include the published Alzheimer's, Drug Abuse, Cardiovascular, Stem Cells databases as well as beta-testing Osteoporosis, Multiple Myeloma, Diabetes databases (www.cbligand.org/CCGS/research.php). His recent work on Alzheimer's disease chemogenomics knowledgebase represents an innovative "data to knowledge" system accessible at www.CBLigand.org/AD/, and won 2014 coverpage story of a top ACS peer-reviewed journal[1]. His lab is developing HD (Huntington), PD (Parkinson) and TBI (Trauma Brain Injury) specific chemogenomiocs database (β-test), implemented with his developed algorithms/tools, including GPU TargetHunter© program for drug target identification (AAPS J special theme issue, www.CBLigand.org/TargetHunter), machine learning Ligand Classifier of Adaptively Boosting Ensemble Decision Stumps (LiCABES) algorithms for GPCR ligand selectivity or functionality prediction, 3D chemistry-space matrix compound library acquisition and prioritization (CLAP) profiling algorithm for constructing/purchasing structural-diverse chemical libraries (2013 *ACS Comb. Science* coverpage), and molecular fingerprint-based artificial neural network for QSAR analysis, HTDocking, and BBB-predictor.

1. Ma, C, Wang, LR, **Xie, XQ*. i)** "**GPU Accelerated Chemical Similarity Calculation for Compound Library Comparison**" ***J. Chem. Inf. Model***., 51 (2011), 1521–1527. ii) "**LiCABEDS II. Modeling of Ligand Selectivity for G-protein Coupled Cannabinoid Receptors**". ***J. Chem. Inf. Model***., 2013, 53(1):11-26
2. Wang L, Ma C, Wipf P, Liu H, Su W and **Xie XQ*.** "**TargetHunter: An In Silico Target Identification Tool for Predicting Therapeutic Potential of Small Organic Molecules Based on Chemogenomic Database**". ***AAPS J.*** 2013, 15**,** 395-406 (**AAPS Special theme issue**)
3. **Xie XQ*,** Wang L, Liu H, Ouyang Q, Fang C and Su W. "**Chemogenomics Knowledgebased Polypharmacology Analyses of Drug Abuse Related G-Protein Coupled Receptors and Their Ligands**". ***Front. Pharmacol****. (Neuropharmacology),* 2014, 5:3.
4. Zhang H, Ma SF, Feng ZW, Wang DY, Li CJ, Cao Y, Chen XF, Liu AJ, Zhu ZY, Zhang JP, Zhang GQ, Chai YF*, Wang LR* and **Xie XQ*** "**Cardiovascular Disease-specific (CVD) Chemogenomics Knowledgebase-guided Target Identification and Drug Synergy Mechanism Study of A Combination of Herbal Medications**." (Nature) ***Scientific Reports***, 2016 Sep 28; 6:33963. doi: 10.1038/srep33963.

4. First INK4C/p18 chemical modulators for hematopoietic stem cell (HSC) expansion

Xie's Lab was the first to discover and report (*Nature Comm* 2015 and *Sci Reports*, 2015) that a small-molecule chemical inhibits $p18^{INK4C}$ (or p18), a stem cell regulator protein and member of the INK4 family of cyclin-dependent kinase (CDK) inhibitor proteins, and that the compound stimulates HSC expansion in murine and human models.

Broad use of hematopoietic stem cells (HSC) is hindered by the limited number of HSC per harvest. Although HSC expansion can be achieved by ectopic expression of several positive regulators via retrovirus or lentivirus-mediated methods, these viral approaches are unfortunately associated with risk of leukemogenesis. Other approaches, including transgenes, cytokines, new protein factors, stromal cells, and bioreactors, have been tested to expand HSCs, but the specificity for HSCs and the efficacy of these approaches in clinical trials have not been determined. Indeed, alternative novel approaches for HSC expansion are still in critical need. We have applied an integrated computational and experimental chemogenomics-based approach and discovered novel p18-targeted chemical promoters of HSC self-renewal, which overcomes the difficulty of performing costly and time-consuming conventional biochemical studies with adult stem cells that are extremely rare in tissues. Thus, using our integrated methods, we have discovered the **first p18 small molecule inhibitors** (**p18SMI) and validated the bioactivities (**ED_{50} = 3.07 μM) by our established *in vitro* and *in vivo* HSC experiments in collaboration with Dr. Tao Cheng, a former faculty at UPCI. We subsequently confirmed the p18 target specificity by performing the Cobblestone-Area Forming Cell (CAFC) assay using long-term (LT) cultures of wild type (WT, $p18^{+/+}$) and knockout ($p18^{-/-}$) murine mouse bone marrow (mBM) cells. Importantly, p18 target specificity of **p18SMIs** was confirmed by a [γ-^{32}P] CDK6 bioactivity assay and co-IP pull down assay. Finally, we confirmed that p18SMIs promoted expansion of both murine and human HSCs in vivo by competitive bone marrow transplantation (cBMT) model, a "gold standard" in vivo functional HSC measurement. p18SMIs did not show significant cytotoxicity toward myeloblast-like 32D cells or primary HSCs, nor did it augment tumor cell proliferation. Thus, our discovered p18SMIs are novel chemical agents for HSCs *ex vivo* expansion and can be used as chemical probes for HSC biology research towards therapeutics.

1. **Xie, XQ*,** Yang P, Zhang Y, Zhang P, Wang L, Ding YH, Cheng HZ, McGuire T, Yuan WP, Cheng T and Gao YD. "**Discovery of novel INK4C small-molecule inhibitors to promote human and murine hematopoietic stem cell ex vivo expansion**" ***Scientific Reports*** (Nature), 2015, 5:18115, DOI: 10.1038/srep18115.
2. Gao Y, Yang P, Shen HM, Yu H, Xie ZJ, Zhang L, Bartlow P, Ji Q, Ding Y, Wang L, Liu H, Ma H, Hao S, Dong F, Li Y, Zhang P, Cheng H, Liang PH, Miao W, Yuan Y, Cheng T* and **Xie XQ*** "**Small-molecule inhibitors targeting INK4 protein p18INK4C enhance ex vivo expansion of haematopoietic stem cells**", ***Nature Communications***, 2015 Feb 18;6:6328. PubMed PMID: 25692908;
3. Zhang Y, Wang, LR, Feng ZW, Cheng T, Gao YD and **Xie XQ*** "**StemCellCKB: An Integrated Stem Cell-Specific Chemogenomics Knowledge base for Target Identification and Systems-Pharmacology Research**", ***J Chem Inf Model***. 2016, 56 (10), pp 1995–2004 DOI: 10.1021/acs.jcim.5b00748

Cheng T, Xie X, Gao Y (Patent) "**p18 small molecule chemical inhibitor and human hematopoietic stem cell (HSC) expansion ex vivo**". ***Patent No***. 201510081641.Publication No: 2015061001183450. 2015-06-12 17:27. **Xie XQ*,** Invited speaker, Nov 2012, "**Novel Small Chemical Inhibitors Targeting p18INK4C Protein for Hematopoietic Stem Cell Expansion**", ***3rd International Forum on Stem Cells***, Tianjin, China

5. BIOASSAY AND ANIMAL STUDIES OF CANNABINOIDS FOR OSTEOPOROSIS AND BONE DISEASES RELATED

Xie has established innovative computational-chemogenomics-knowledgebase-guided CB2-mediated signaling mechanism studies and system pharmacology research as well as in vitro osteoclast and in vivo ovariectomized (OVX) rat osteoporosis model experiments through collaboration with D Roodman and D Gilson (see their letters). Due to the interactions between myeloma cells and cells of the bone marrow microenvironment, the **osteoporosis (OP)** or osteolytic bone disease associated with **myeloma** is inextricably linked with tumor progression. High incidence of bone metastasis in MM patients (95-100%) is associated with severe bone pain and pathological fracture (60%), which has been defined as the result of activated osteoclast and suppressed osteoblast. With many years of developed research investigations and how-know technologies, we have found that high levels of expression of active CB2 were observed in human MM cell lines and primary CD138+ myeloma cells. Our discovered CB2 ligand, phenylacetylamide (PAM, or XIE95), inhibits MM growth through cell cycle modulation, mitotic death and cytoskeleton disruption. In particular, our studies show that CB2 gene silencing rescues PAM-induced inhibition of MM cell proliferation. Furthermore, it's been reported that CB2 is expressed in osteoclast and osteoblast as well as their precursor cells. CB2-/- mice showed accelerated age-related trabecular bone loss and cortical expansion. CB2-/- osteoclast number and trabecular osteoblast activity were increased. The role of CB2 pathway is important in MM-induced bone remodeling. We found that our compound favorably suppressed osteoclast formation in both murine and human osteoclastogenesis. Our top CB2 compounds demonstrated promising therapeutic index by animal efficacy and toxicity laboratory studies.

1. Feng R, Tong Q, Xie Z, Wang L, Lentzsch S, Roodman GD, **Xie XQ***: Targeting cannabinoid receptor-2 pathway by phenylacetylamide suppresses the proliferation of human myeloma cells through mitotic dysregulation and cytoskeleton disruption. ***Mol Carcinog*** 2015:PMID: 25640641
2. Feng RT, Milcarek CA, **Xie XQ***: Antagonism of cannabinoid receptor 2 pathway suppresses IL-6-induced immunoglobulin IgM secretion. ***BMC Pharmacol Toxico*** 2014, **15**:30 PMID:24913620.
3. Gertsch, J.; Leonti, M.; RadunerS.; RaczI.; Chen, J.-Z.; **Xie, X.-Q.**; Altmann, K.; Zimmer, A.; Karsak, M. Beta-Caryophyllene is a Dietary Cannabinoid. ***PNAS*** **105**(2008), 9099-9104.

6. METHOD DEVELOPMENT OF ADVANCED ISOTOPE MEMBRANE PROTEIN ENGINEERING FOR GPCR CB2 RECEPTOR STRUCTURE STUDY AND STRUCTURE-BASED DESIGN.

G protein-coupled receptors (GPCRs) are considered as one of the most important ***nanobiological proteins with a size of 4 nm***, and have become even more important as drug targets since the completion of the human genome and proteome initiatives. The objective of this project is to d***evelop*** the novel membrane protein biosynthesis approach-"*Segments to 3D GPCR Construct*" through a ***multidisciplinary research work*** using the combined: i) microbiology/recombinant protein engineering, ii) *E. coli* overexpression/isotope labeling, iii) purification chemistry, iv) advanced NMR biophysics and v) computer modeling techniques. His group has accomplished the followings:

- Xie was the first to report the high yield over-expression and purification of hydrophobic transmembrane CB2 protein fragments and introduce the unique enzyme/chemical cleavages methods to remove the fusion tag from water-insoluble fusion proteins as well as refolding target proteins. This article won the top 20 paper award in 2004 for the journal over 10 millions registered users. As quoted by the Elsevier Sciences Journal editor, "this award recognized the popularity and interests/values of your research work to the others in the field." (*Protein Exp. & Purif.* 2004).

- Xie was the first to report the application of a proprietary *E. Coli* overexpress system for CB2 membrane protein fragment expression and purification – that *overcome the cellular toxicity* associated with recombinant membrane proteins (*J. Peptide Research, 2005*).

- Xie has prototyped the experimental protocols for isotope labeling, GPCR CB2 membrane protein purification and refolding, which overcome *the cellular toxicity* associated with recombinant membrane proteins (*J. Peptide Research, 2005; Protein Exp & Purif 2008)*

- Xie has established 2D/*3D NMR methods* for characterization of CB2 membrane protein and fragments refolded in membrane-mimic environments (*2005 MALTO Meeting, the best poster presentation award to Xie's student Mr. Sheng*).

- Xie has reported his *extensive computational biology studies* of the structural properties of the 3D CB2 receptor structure and *biologically important microdomains* - the conserved residues/motifs within the receptor binding sites, in combining with NMR experiments (*Proteins 2003, JBC 2005, Protein & Peptide Letters 2006*). In addition, Xie has conducted 3D Flexible ligand dock and established GPCR CB2 receptor-based in-silico design/virtual screening/CScoring algorithm for CB2 antagonists (*JCIM 2007*).

- Establish a new international collaborative project - NIH Roadmap Initiative Structural Biology RFA-RM-04-026 R01 (X.-Q. Xie, P. I.) "*De Novo Biosynthesis of G-Protein Coupled Receptor for Structural Studies*" (Developing a novel approach to over-produce GPCR membrane proteins by using Semliki Forest Virus (SFV)-based mammalian cell system for functional expression of GPCR).

Overall, the structural and conformational data will guide to assemble the 3D nanostructured CB2 receptor and exam it further for its structural biology. Such studies will provide ***valuable experimental data to refine the 3D construct of the CB2 receptor***, an experimental-based 3D CB2 structure that will be a more ***reliable 3D model*** for rational drug design. The work accomplished can potentially make a *significant contribution* to membrane protein NMR structural biology as well as GPCRs, a large family of drug targets (~45% of the market drugs).

7. INTEGRATED NMR AND COMPUTER MODELING FOR CB2 LIGAND IN-SILICO DESIGN AND VIRTUAL SCREENING

Xie has establish a *novel GPCR chemical genomics CB2* drug research by using combined NMR/computational studies of the target drugs and their interaction with the GPCR receptor for rational drug design as well as building an in-house 3D pharmacophore ligand-search database. The developed 3D pharmacophore database search can be carried out as a "*pre-screen*" or "virtual screen" before the costly experimental bio-testing of large numbers of compounds in order in order to generate a *structurally diverse set* of molecules to investigate and accelerate discovery of *new CB2 drug-like leads.*

Xie and his group have also established computer-aided pharmacophoric correlation methods and numerical delineations of the 3D molecular structure and biological activity of these ligands and derive the active sets of pharmacophore models that are currently used in 3D pharmacophore-based in-silico screening. Xie has illustrated them as below:

- Xie was the first to report the NMR-based 3D QSAR/Comparative Molecular Field Analysis (CoMFA) studies of arylpyrazole antagonists of CB1 and CB2 cannabinoid receptors(*JMC 2006*). Xie also conceptualized the "three-points" pharmacophore model for CB ligands (Xie, et. al. *JMC,1994*); and established a "ligand-membrane-receptor" activation pathway (*Xie, et. al. JBC, 1996*).
- Xie was also the correspondent author of the published work on a combined NMR/computational studies of anandamide, a very important endogenous cannabinoid ligand, and synthesis of

arachidonylethanolamine (AEA) analogs (*Life Sciences 2005);* He also collaborated with others to investigate the anandamide transporter (*PNAS 1999*). Dr. Xie also applied multi-dimensional pulse gradient NMR and solid-state REDOR NMR and computer dynamics simulation to study endogenous and synthetic CB ligands (*J. Pep. Res. Xie*).

- Xie was the first author of the published work on 3D CB2 receptor structural model using homology and multiple sequence alignment as well as MD/MM simulations (*Proteins 2003*).
- Xie was the first author of the published work on 3D conformation/structure of aminoalkylindoles (AAIs)-type cannabinoid ligand, WIN55212-2. WIN55212-2 is one of the most potent cannabinoid ligands. Its radioligand form has been used widely in high-throughput drug screen and receptor binding assay (*JMC 1999*).
- Xie was the first author of the work on conformational properties of CP-55940 by NMR-based computer modeling approach. CP-55940 is considered as one of the most important cannabinoid ligands because of its pivotal role in the discovery of the cannabinoid receptor, and has been widely used as the radioligand of choice for cannabinoid receptor binding and drug screening assay today (*JBC 1996*).
- He also launched a new NIH Roadmap RFA-RM-04-027 proposal "*Pharmacoinformatics Research Center*" (PRC) (Xie, X.-Q., P.I. and scientists from the six GCC institutions) to establish an exploratory center for "Pharmacoinformatics" research - a new interdisciplinary research field emerging from the integration of the approaches of pharmacology and biology with newer computational methods of bioinformatics and cheminformatics) (unfunded).
- Dr. Xie also received his second R01 grant to build "*A Public Cannabinoid Molecular Information Database Repository System*" R01 DA/LM15417 (X.-Q. Xie, the P.I.). The R01 is to d*evelop a proprietary public molecule information database* (cannabinoids as a startup domain) with online structure drawing and 3D view/rotating features; integrating them but also designing and implementing a computational environment that facilitates the repository's future growth; to construct *a unique flexible and easy-to-use query interfaces for the database*; incorporate the newest data exchange technology, XML, into the database to ensure database portability and future expansion. Advance data mining/algorithm in pharmacoinformatics.
- NIH SBIR R43DA016823 (X.-Q. Xie, P.I.),"***GPCR ligand info repository and In-Silico Design***" Phase I: $100,000, 07/01/04 - 06/31/05; Phase II: $700,000 (3 year) (Scored 254).

8. COMPUTATIONAL CHEMICAL GENOMICS SCREENING CENTER.

As Founding Director, Xie has taken a lead to establish a new center at University of Pittsburgh "Computational Chemical Genomics Screening (CCGS) Center. The **overall goal** of the proposed CCGS Center is to build a research/teaching and collaboration platform by providing innovative computational tools/algorithms and chemical library resources in the genomics-scale for *in-silico* drug design and discovery. This goal is related to, but distinct from, cheminformatics, computational biology, bioinformatics, medicinal chemistry and pharmacology. The **objective** is the more rapid identification of novel drug-like molecules, so called "lead compounds," and their associated biological targets embracing multiple early phase drug discovery processes ranging from *in-silico* drug target identification and validation, to *virtual* screening, lead modification/scaffold hopping and virtual compound library design, and then to *in silico* ADME profiling. CCGSC will have a **mission** to promote interdisciplinary research, education and training, and foster collaborations to develop state-of-the-art computational-chemical-genomics-based *in-silico* drug design approaches through exploration of chemical-diversity space and its relationship to biological space.

The CCGS Center has developed/published compound-library-profiling algorithms, virtual chemical genomics library, GPU-accelerated molecular fingerprint calculations, as well as our computational chemical genomics approach, we have successfully applied and discovered/patented several important lead compounds for specific targets and biologically validated in-house or through collaborations with MDs at UPMC or other institutes. These identified drug leads are being used as important chemical probes for mechanism of drug action and cell signaling studies. Among the lead compounds show promising therapeutic potential, below are some illustrations of our recent successful research work, including:

- Novel GPCR CB2 leads and druggable compounds for breast cancer and osteoporosis (patent, NIH grant pending).
  Patent: Xie, X-Q*., J.Z. Chen and Y.X. Zhang. "Ligands Specific for Cannabinoid Receptor Subtype 2" (2009), WO 2009058377, 2008-US12395, 2007USSN 60/984,461.
- P62zz domain inhibitor, a first chemical probe discovered, potential for multiple myeloma (patent, conference).
  Patent: Xie, X-Q.*, Myint, K. Roodman, D. "P62-ZZ Chemical Inhibitor" (2011). US 61/521,287
- Novel DNA damage repair protein APE inhibitors (patent, Biochemistry paper, NIH grant pending).
  Patent: Gold, B. and **Xie, X-Q**, "Inhibitors of AP endonuclease-1/redox factor-1 (hAPE1) activity." PCT/US2013/023653, USSN: 61/593,276, Pitt Ref. No. 02385 and **a joint publication** "The Identification and Characterization of Human AP Endonuclease-1 Inhibitors". Biochemistry 2012 (51), 6246-6259. PMID: 22788932.
- p18-target chemical drugs for hematopoietic stem cell expansion (new NIH grant, scored 6 percentile).
  *Patent: Xie, X-Q and Cheng, Tao et al. "$P18^{INK4}$ Inhibitor for Hematopoietic Stem Cell Self-Renewal" pending
- Novel Atg4B inhibitor for cancer autophagy signaling (patent, NIH grant submitted)
- Patent: Yin, XM and **Xie, X-Q**, "Modulation of Autophagy by Atg4B inhibitors" Int. Reference 02204
- Other projects (autoimmune with UPMC immunology, PTH ligands with UPMC VA, DMP1 inhibitors with UP Dental School, etc).

9. CCGS Center Core Technologies. The success above was built based on our developed/published computational algorithms and tools, as well as structurally-diverse and target-focused libraries. These are the core technologies and available resources of the CCGSC as illustrated below. We have developed/published and also make these technologies and products, including software programs/tools and structurally-diverse or target-focused libraries, available via either direct services or collaborations. The most recent collaborations ongoing include FOXO1 inhibitor design and screening (Dr. Henry Dong at UPMC Children hospital), NCI contract via UP-CDC (Dr. Donna Huryn), GPU-accelerating big library comparison computing (Dr. Christian Herhaus at Merck KGaA-Germany), etc.

- **Web-interfaced drug or chemical repository architecture**. We have designed and constructed user-friendly web-interfaced small molecule database to facilitate the data sharing and information exchange among the members. See as an example the largest cannabinoid ligand database in the world (www.CBLigand.org/CBID), designed and constructed by Dr. Xie's lab. We can apply the database schema to build another domain specific chemical library, such as stem cell chemical drug database.

- **Structurally-diverse or target-focused chemical libraries**. Over years, we have acquired many public and vendor based compound libraries, converted them to 3D molecular databases and then re-classified them into *structurally diverse and target specific* virtual libraries that ultimately represent full genomics-scale chemical libraries to facilitate virtual chemical genomics screening. Such libraries launched by Xie's lab are listed as examples below:
  - www.CBLigand.org/gdb13: World largest online chemical database (1 billion)
  - www.CBLigand.org/UPCMLD: A chemical biology metabase for NIGM funded University of Pittsburgh UPCMLD, UPCMLD-ChemBioDB
  - rePubChem. **(Xie** et al., "Data-mining Small Molecule Drug Screening Representative Subset from NIH PubChem. *J.Chem. Inf. Modeling*, **48**(2008), 465-475)
  - **Compound Library Acquisition and Prioritization (CLAP) Algorithm** for strategically purchasing new chemical compounds with maximized structural diversity. www.CBLigand.org/CLAP (Xie, et al "Compound Library Acquisition and Prioritization

(CLAP) Algorithm for Constructing Structurally Diverse Chemical Libraries. J. *Comb. Chem.* **13**(2011), 223-231)

- **Diversity-oriented synthesis (DOS) Prioritization (DOSP) algorithm** for selecting or prioritizing a diverse subset from a large combinatorial chemical library before costly synthesized (Xie, et al "Diverging DOS Strategy Using an Allene-Containing Tryptophan Scaffold and a Library Design that Maximizes Biologically Relevant Chemical Space While Minimizing the Number of Compounds." ACS *Combinatorial Science* **13** (2011), 166-174; "A Diverging Rh(I)-Catalyzed Carbocylization Strategy to Prepare a Library of Unique Cyclic Ether." *J. Combin. Chem.* **10** (2008), 235-246).

- **Target Identification and virtual screening.** With computational systems biology, virtual chemical genomics screening algorithms and data mining tools, CCGSC provides a research platform and collaboration services for biological target identification and the expertise to screen/identify druggable compounds or leads. Some of our developed computational chemical genomics tools and algorithms are illustrated below (see http://www.cbligand.org/xielab/technology.php).
  - **Ligand pharmacophore-based 3D database search approach** (Xie, et al. "3D QSAR Pharmacophore Studies of Arylpyrazole Antagonists for CB1 and CB2 Cannabinoid Receptors. A Combined NMR and CoMFA Approach", *J. Med. Chem*. 49 (2006), 625-636; "Beta-Caryophyllene is a Dietary Cannabinoid." *Proc. Natl. Acad. Sci. USA* **105** (2008), 9099-9104; "Fragment-based QSAR Algorithm Development for Compound Bioactivity Prediction", *SAR and QSAR* **13**(2011), 223-31)
  - **Receptor structure-based virtual screening approach** (Xie, et al "Residue Preference Mapping of Ligand Fragments in PDB" . *J. Chem. Inf. Modeling*, **51** (2011), 807-815; "GPCR structure-based virtual screening approach for CB2 antagonist search." *J. Chemical Information and Modeling,* **47** (2007), 1626-1637; "3D Structure Model of the G-Protein Coupled CB2 Cannabinoid Receptor" *Proteins: Structure, Function, and Genetics,* **53** (2003), 307-319)
  - **New computational algorithms and software** for virtual hit selection and ligand function classification:
    - High Throughput Docking virtual screening www.CBLigand.org/HTDocking
    - Ligand Classifier of Adaptively Boosting Ensemble Decision Stumps (LiCABEDS). Novel machine learning algorithm for compound biological classification prediction: www.CBLigand.org/LiCABEDS (Xie, et. al. "LiCABEDS (Ligand Classifier of Adaptively Boosting Ensemble Decision Stumps). A Machine Learning Based Algorithm for GPCR ligand selectivity and functionality predictions." *J. of Chem. Inf. and Modelings* **51**(2011), 521-531)
    - Web-interfaced GPCRs functionality predictor designed using machine learning SVM and KNN algorithms. www.CBLigand.org/5HT1A (Bioinformatics, accepted)
    - False Positive Remover. Help to identify the false positive hits from high throughput screen experiments. www.CBLigand.org/FPR
    - Off-target Predictor to help characterization of off-target activities of a drug molecule and TargetHunter to identify new drug target. www.CBLigand.org/TargetHunter

- ADME computing algorithms and tools (ongoing projects) to predict the ADME properties of drug lead compounds:
  - **BBB-permeability predictor** to predict drug or chemical compound permeability to cross blood brain barrier. www.CBligand.org/BBB
  - **iADME***. In silico* ADME predictor. (ongoing research work)
  - GPU-accelerated molecular property calculation. www.CBLigand.org/gpu (Xie, et. al. "GPU Accelerated Chemical Similarity Calculation for Compound Library Comparison" JCIM, **51** (2011), 1521–1527)
  - Fragmemt-based QSAR, PharmShape based QSAR etc (Xie, et. al. "Fragment-based QSAR Algorithm Development for Compound Bioactivity Prediction", *SAR and QSAR in Environmental*

Research **13**(2011), 223-31; "3D QSAR Studies of Arylpyrazole Antagonists for CB1 and CB2 Cannabinoid Receptors. A Combined NMR and CoMFA Approach", *J. Med. Chem.* **49**(2006), 625-636)

We continue to carry out our ongoing virtual screening algorithm design and development, pharmacophore model studies and screening hit selection/score function development. We also team up with pharmacologists/biologists for lead biovalidation using in vitro bioassays, with medicinal chemists for lead modifications/optimizations, and with pharmaceutics and clinical toxicology specialists for ADME prediction and further validation of novel leads towards new drug design and discovery.

D. TEACHING AND STUDENT LEARNING

a. Post-doctoral Fellow and Visiting Scholar Training:

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b. Graduate Student Training:

i. As Major Advisor – Master and /or Doctoral supervision

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ii. As Invited Thesis Committee Member/Associate Advisor

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iii. As Graduate Student Research Rotation Advisor

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iv. As Undergraduate Student Training Advisor (including Pre-MD students)

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<u>c. Pharm D. Professional and Graduate Courses Taught</u>

1. Pharmacometrics & System Pharmacology (PSP), a new MS Graduate Program.

Inspired by the recent Pharma/Biotech drug discovery and development, Dr Xie has proposed and also obtained an approval for School Budget & Planning Committee and Graduate Curriculum Committee, and established a MS program focusing on pharmacometrics and systems pharmacology (PSP) education. It is called PSP instead of quantitative systems pharmacology (QSP) as clinical data analysis is also an essential part of the MS program. The PSP MS program and our NIH-funded Center and Core, CDAR and CCGS, are mutually benefited. On one hand, CDAR and CCGS provide our graduate students golden opportunities to gain the knowledge and to build expertise on the state-of-the art “big-data” pharmacometrics and computational systems pharmacology, as well as to learn the cutting-edge techniques on drug discovery and drug development that will enhance their career development. On the other

hand, our CDAR and CCGS will achieve more exciting progress on our PSP research with more excelling students who are well-trained in the PSP program joining our team.

The Pharmacometrics and Systems Pharmacology (PSP) program within Pharmaceutical Sciences focuses on applying computational pharmacometrics and computational system pharmacology techniques to advance the preclinical and clinical research by the development of novel drug candidates that are less likely fail during the clinical trials and better understanding the mechanisms of drug actions and therapeutic effects at the systems pharmacology level.

- You will learn and acquire a broad knowledge and hands-on experience of applying pharmacometrics and systems pharmacology to design and develop drug candidates that are less likely fail in clinical trials.
- You will develop strong computational modeling and simulation expertise from drug target fishing, to drug lead identification, to drug profile optimization (e.g. ADME-Tox and bioavailability) and PK/PD modeling.
- You will master skills on developing multi-scale computer models (both data-driven and model-driven) that describe drug actions at multi-levels of molecules, genes, organs, and organisms.
- Your will have opportunities to conduct research studies with faculty from a variety of background including computer-aided drug design, computational and system biology, population PK/PD modeling, PBPK, computational chemical genomics, computational biophysics, etc.
- Student applicants majoring in Pharmaceutical Sciences, Chemistry, Biology, Bioinformatics, Statistics, Computer Sciences and Biophysics/Biochemistry are encouraged to apply.

Two Core Courses developed under the program director Dr Xie:

PSP I (PHARM 3068) Computational Systems Pharmacology
Course Description

This course will teach the fundamentals of computational systems pharmacology (CSP) modeling and their applications to study drug actions and rational development of new drugs through network analysis. Theoretical concepts pertaining to computational systems pharmacology, such as drug target identification and rational drug design, will be taught. The course also includes hands-on training with the mainstream network analysis and computer-aided drug design software, such as Symbiology of Matlab, Tetrad, the drug discovery package of Schrodinger.

PSP II (PHARM 3069) Pharmacometrics
Course Description

This course will provide training in the fundamentals of pharmacometrics & systems pharmacology (PSP) modeling and their applications to study drug actions through multiscale modeling and simulations [mechanism-driven] and data analysis [data-driven]. Theoretical concepts pertaining to PSP, such as population pharmacokinetics/pharmacodynamics (pop PK/PD) modelling both from mechanistic and statistical points of view, physiologically-based pharmacokinetics (PBPK) data analysis, will be taught. The course covers the advanced pharmacokinetics/pharmacodynamics (PK/PD) topics, such as drug-drug interactions, disease progression, as well as multi-scaling PK/PD modeling of drug actions for selected diseases, including cancers, type 2 diabetes, etc. The course also offers hands-on training on using mainstream population PK/PD and PBPK modeling and simulation software.

2. Courses Taught Time spent

University of Pittsburgh

Pharm3048 "Drug Discovery, Design & Development Journal Club" (1 credit) as course coordinator**,** 21 hours course time. 2013 Spring. 2014 Spring, 2015 Spring, 2016 Spring, 2017 Spring

Advanced Medicinal Chemistry (Pharm3032) (3 credits) lectured 8 hours on Computational Medicinal Chemistry, 2009, 2010, 2011, 2012, 2013, 2014 Fall.

Foundations in Pharmaceutical Sciences (Pharm3023) (5 credits) as a course co-coordinator (Part II. Drug Discovery and Design) and lectured 6 hours on computer-aided drug design, 2009 Spring and 2010, 2011, 2012, 2013 Spring. 2014 Spring

PHARM2100 Pharmaceutical Analysis (3 credits), taught 14 hrs lectures - NMR application in pharmaceutical sciences, 2009 Spring, 2010 Spring, 2011 Spring, 2012, 2013 Spring.

Pharmacogenomics (Pharm 3020) (3 credits), taught 8 hrs lectures and exam on GPCR Cell Signaling in pharmaceutical sciences, 2008 Spring.

Drug Discovery (MSMPHL 2370) (2 credits), taught 4 hrs lectures and exam on Computational Chemical Genomics in Drug Discovery Institute, 2008 Spring

Essentials of Grant Writing (Pharm3038/3039) (2 credits), 8 hrs including reading student grant writings and interview exams, 2008 Spring

University of Houston:

UH PHAR4350 PHARMACY SKILLS PROGRAM I- **Functional Groups (PharmD**.) (3 credits, 125 students), taught 48 hrs (40%), Fall 2004 and 2005, covering the knowledge and problem solving skills in drug physical and chemical properties and drug metabolism. Xie has introduced "Jeopardy games" into the lectures to promote the active learning opportunity. His teaching was well liked by the Pharm D students (see the supporting materials in Appendix A).

UH PHAR4351 PHARMACY SKILLS PROGRAM II - Functional Groups (PharmD.) (3 credits, 125 students), taught 15 hrs (12%), Spring 2005, covering the knowledge and problem solving skills in drug chemical and physical properties and drug metabolism.

UH PHARM4401 Cellular Life Sciences II (PharmD.) (4 credits , 125 students). Taught 4 hrs in Spring 2005 covering Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (Chemistry, Metabolism, Drug Structure Activities).

UH PCOL6398 Graduate Student Special Problems/Independent Study (3 credits, 3 students), 30 hrs(100%), summer, Fall 2004.

UH PCOL6398 Graduate Student Special Problems/Independent Study (3 credits, 2 students), 60 hrs(100%), Spring, Summer, Fall 2005.

UH PCOL6398 Graduate Student Special Problems/Independent Study (3 credits, 3 students), 30 hrs(100%), Spring 2006.

(Planned) **UH PHAR7130 Pharmacoinformatics and Structure-based Drug Design**. This course is designed from graduate students majoring in Medicinal Chemsitry and also is a NIH Pharmacoinformatics Training Program Course for graduate course. Xie will serve as a course coordinator.

University of Connecticut:

UC Ph.D. research and deserrtation work course GRAD499 (6 credits, 2 students), 60 hrs, 2002-2004.

UC Introductory NMR and Practical Techniques (100%). Xie gave a intensive NMR course every semester including summer, and provide instruction for those who want to have an access to use the NMR spectrometers for their research. Xie always mad time available to students or faculty who need assistance/discussion on the projects. He was proven to be a patient and resourceful teacher, and is very well liked by the students. 1996-2003

UC PHARM318/Independent Study (3 credits). 40 hrs (100%). Full responsible lecturer for graduate student special topic course

Special topics: GPCR Structures and Functions 2002
Drug Database Screening Search Algorithm Evaluation, 2001

UC CHEM345 (Determination of Organic Structures) (3 credits), 10 hrs (12%) 1996
Lecture: taught spectroscopic instrumental analysis

UC CHEM381 (Polymer Physical Chemistry) (3 credits), 8 hrs (10%) 1997
UC CHEM382 (Polymer Characterization I) (3 credits), 16 hrs (20%) 1998, 1999
Lecture: gave lab demonstrations on NMR experiments.

UC PHARM301 (Drug Design) (3 credits), 8 hrs 1995, 1999
Lecture(10%): team-taught graduate students, responsible for teaching NMR and computer modeling approach for rational drug design.

UC PHARM315 (NMR Applications in Medicinal Chemistry) (3 credits), 24 hrs 1995
Leading lecturer (40%) in teaching graduate students in PHARM315 and lab course: Applications of NMR in Medicinal Chemistry.

UC PHARM208 (Physico-Chemical Principles of Drug Systems II) (**Pharm D**) (4 credits) 1994-24 Lecture(25%): team-taught undergraduate students in PHARM208: instrumental analysis, and identification and analysis of drug molecules.

UC PHARM209 (Physico-Chemical Principles of Drug Systems III)(**Pharm D**.) (3 credits) 1989-, 1991,1993
Teaching Assistant(50%): taught 1-hour pre-lab lecture per week and supervised 3-hour laboratory per week as well as lab discussions and correcting laboratory reports.

UC PHARM213 (Physico-Chemical Principles of Drug Systems V)(**Pharm D.**) (3 credits) 1990-, 1992
Teaching Assistant(50%): taught 1-hour pre-lab lecture per week and supervised 3-hour laboratory per week as well as lab discussions and correcting laboratory reports.

UC CHEM128 (General Chemistry) (Undergraduate course) 1987,1988
Teaching Assistant(50%): taught chemistry Laboratory and Discussion course, included pre-lab lectures, lab discussions and correcting laboratory reports.

China Pharmaceutical Analysis Course (Pharm BS) 1983 to 1986
Lecture: taught undergraduate student course in Pharmaceutical Analysis at the College of Pharmacy, Second Military Medical University, Shanghai, P. R. China, including UV, IR, GC, HPLC, MS and NMR methods for qualitative and quantitative analysis of drug molecules. Xie was the recipient of the Outstanding Teacher Award from the university in 1984.

E. PROFESSIONAL SERVICE

Dr Xie is a member of the Science Board to the US FDA. He is an Editorial Advisory Board member for AAPS Journal and American Journal of Molecular Biology, and Associate Editor of BMC Pharmacology Toxicology. He was a Charter Member of NIH BPNS Study Section, *ad hoc* expert reviewer for UK MRC foundation, the Wellcome Trust Fund, the Netherland Organization for Scientific Research Council, the Austrian Science Fund (FWF) Erwin Schrödinger Fellowship, and the Chinese Natural Science Foundation. He holds/held honorary professorship in top institutes and colleges of pharmacy in China, including Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin Stem Cell Medical Center; and Shanghai Jiaotong University. He was an invited International Assessment Panelist for Fudan University, a member of the Board of Directors of the Chinese Association of Professionals in Science and Technology, and a Chair of the CAPST-Biomedical & Pharmaceutical Society. He is also a member of Science Advisory Board to Oxis Biotech.

The professional services are illustrated below (see page 7 for details):

2016 – present	**Editorial Board Member of AAPS J** (American Association of Pharmaceutical Scientists)
2015/1-2018/1	**Charter Member of FDA Science Board Committee**, the United States Food and Drug Administration (2014-2018)
2015/8	***Ad Hoc* Expert Reviewer** of the Austrian Science Fund (FWF, *Fonds zur Förderung der wissenschaftlichen Forschung*) Erwin Schrödinger Fellowship
2015/5	**Review Team** of Graduate Program Review Site Visit for Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston Texas
2015/3	**NIH Site Visit Panelist** of P41 Program Project (ZRG1 BCMBS 40) for National Resource for Dynamic Protein NMR Structures and Complexes NIH Site Visit Review
2015/1	**Member** of Science Advisory Board to Oxis Biotech.
2013/10	**Invited Keynote Speaker and Session Chair**, 2013, 144th OMICS Group Conference, 2nd International Conference on Medicinal Chemistry & Computer Aided Drug Designing (MedChem & CADD-2013), Las Vegas, USA
2013/7 2015/7	**Invited Oversea Expert Panel Reviewer** for Chinese Natural Sciences Foundation (CNSF) Key Grant Review Panel Meeting for Pharmaceutical Sciences Key Program, Beijing, China
2013/3	**IAR Reviewer Invitation** for ZRG1 BST-J (40) P - PAR-11-220 NIGMS Program Project Review - Special Emphasis Panel/Scientific Review Group.
2012/12	**Invited grant reviewer** for Netherlands Organization for Scientific Research (NWO), Council for Chemical Sciences (CW) (http://www.nwo.nl/en/funding/research+funding)
2012/8	**Invited Reviewer**, The Wellcome Trust Fund, Sir Henry Wellcome Fellowship, London, UK (http://www.wellcome.ac.uk/Funding/Biomedical-science/Funding-schemes/Fellowships/Basic-biomedical-fellowships/wtx033549.htm)
2012-	**Associate Editor and Editorial Board Member** of BMC Pharmacology and Toxicology http://www.biomedcentral.com/bmcpharmacoltoxicol/about/edboard *(Impact factor*: 3.15)

2012	**Invited Grant Judge** of Intel International Science and Engineering 2012 (http://www.societyforscience.org/intelisef2012)
2011	**Invited Guest Editor** of *American Association of Pharmaceutical Scientists (AAPS) Journal*, 2011 Theme Issue "New Paradigms in Pharmaceutical Sciences: In Silico Drug Discovery". www.pharmagateway.net/ThemedIssuePage.aspx?JournalID=12248&CategoryID=1231 (*Impact factor*: 5.714)
2011 – pres	**Charter Member** of NIH Biophysics of Neural Systems (BPNS) Study Section Review Panel (http://internet.csr.nih.gov/Roster_proto1/member_roster.asp?srg=BPNS&SRGDISPLAY=BPNS&CID=103011)
2011/7 -	**Editorial board Member** of American Journal of Molecular Biology www.scirp.org/journal/EditorialBoard.aspx?JournalID=532 .
2010/6	**Invited International Expert Reviewer** of Research Grant for the Molecular and Cellular Medicine Board (MCMB), Medical Research Council (MRC) Foundation, United Kingdom (http://www.mrc.ac.uk/Sciencesociety/MRF/index.htm)
2010/5	**Session chair/invited speaker**, International Medicinal Chemistry Symposium, Beijing, China (http://www.bitlifesciences.com/icm2010/default.asp)
2010/2	**Ad hoc Reviewer** of NIH Macromolecular Structure and Function D Study Section (MSFD) review panel
2010/2	**Invited Special Emphasis Panelist** for NIH National Institute on Drug Abuse (NIDA), "Targeted Library Synthesis and Screening at Novel Targets for Potential Drug Addiction (R21/R33)" (ZDA1 MXL-F)
2009/12	**Invited International Assessment Panelist** for Fudan University College of Pharmacy (one of the five international IAP members).
2009/10	**Invited External Reviewer** for Faculty Promotion in Jordan Applied Science Private University, Amman, Jordan
2006-2011	**Invited Expert Panel Reviewer** for Chinese Natural Sciences Foundation (CNSF) grant review panel meeting for Pharmaceutical Sciences Program, Beijing, China
2007-	***Ad hoc* Reviewer** of NIH Biomedical Library and Informatics Review Committee (BLIRC), National Library of Medicine
2006-	**Member** of NIH grant Center for Scientific Review *Biophysical and Biochemical Science Study Section* (ZRG1 F04B)
2008- 2010	**Chair** of the Graduate Admission Committee, and a member of Graduate Program Council, School of Pharmacy, University of Pittsburgh.
2008/10	**Chair** and **invited speaker**, 2008 International Drug Discovery and Technology Symposium: "GPCR Technology and Drug Discovery", Beijing China. (http://www.iddst.com/iddst2008/ScientificProgram.htm)
2008-	**Chair** of the Distinguished Lecture Series Committee, School of Pharmacy, University of Pittsburgh.

2008	**Committee Panel Meeting**, invited to NIH MLSCN Steering Committee Meeting, Albuquerque, NM
2008	**Advisory Panel Meeting**, invited to NIH Roadmap Committee Meeting: Defining the Role of Informatics within the Molecular Libraries Program (MLP), Bethesda, MD
2007-	**PI and Director** organizing NIH X02 PAR-07-353 CRC Center Grant – a collective cross-campus and cross-institution initiative to build Pittsburgh Cheminformatics Research Center (UPitt, PSC, and CMU) http://grants1.nih.gov/grants/guide/pa-files/PAR-07-353.html)
2006-	**Committee member and Co-PI** of NIH funded Pittsburgh Molecular Library Screening Center (PMLSC) and Drug Discovery Institute (DDI)
2006(10/19-22)	**Chair** and a leading organizer for 2006 American Chemical Society (ACS) Southwest Regional Meeting – NMR Symposium "Challenges of NMR Structural Proteomics", Houston, Texas.
2006(5/21-5/23)	**Faculty Chair** and an organizer for the 2006 MALTO meeting – Medicinal Chemistry and Pharmacognosy meeting at Houston, Texas.
2005-2006	**Member of the Board of Directors** of the Chinese Association of Professionals in Science and Technology (CAPST)(中国旅美专家协会) and a **Chairperson** of the CAPST-Biomedical and Pharmaceutical Society(医药生物工程学会).
2004-2006	**Member of the Advisory Steering Committee** for NIH Pharmacoinformatics Training Program at Houston – Gulf Coast Consortia
2004-2006	**Member of the Curriculum Committee** for the College of Pharmacy University of Houston, Texas
2004-	**Member** of the International Structural Genomics & Rationale Drug Design on Membrane Proteins Consortia (Dr. Kenneth Lundstrom), Switzerland
2004-2006	**Committee Member** for development of the Clinical Track Faculty Policy, College of Pharmacy, University of Houston
2004-2006	**Committee Member** of Information Technology, College of Pharmacy, University of Houston
2004- 2006	**Director** of Chemistry Coordinating Center – Chemistry Unit of the new GCC initiative – Chemical Genomics Screening Center Houston
2004-2006	**Informatics Advisory Committee member** of GCC Regional Small Molecules Library Screening Center, Houston
2004-2006	**Committee member** of Keck NMR Facility, University of Houston
2004	**Dept Chair Search Committee Member**, PPS, College of Pharmacy, UH, Houston
2001-2003	***Ad Hoc* Reviewer**, intramural grant University of Connecticut
2002/3	***Ad Hoc* Reviewer**, NIH, Cutting Edge Basic Research Award (CEBRA) Program

2001-	***Ad Hoc* Reviewer**, Peer-review Journals, Journal of Biophysics, Biochemistry, Proteins, Protein Expression and Purification, J. Medicinal Chemistry, Life Science, J. Peptide Research etc.);
2002	**Consultant,** Boston Scientific Corp, Natick, MA.
2000	**Consultant**, Pfizer Company, Groton, CT
2001	**Consultant**, Arch Chemical, Inc., Cheshire, CT
1999	**Consultant**, Roger Chemical Company, Norwich, CT.
1998	**Consultant**, Jeneric/Pentron Inc., Wallingford, CT
1998	**Consultant**, Uniroyal Chemical Co. Inc., Middlebury, CT
1997	**Consultant**, Enthone - OMI Inc., New Haven, CT