**DESC0002032**

# DOE Integrated Research Training Program of Excellence in Radiochemistry

## Washington University School of Medicine


## Principal Investigator:
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## Funding Period:
## 09/01/2009-08/31/2014

## $2,132,097.00 Total Costs

## Project Summary/Abstract

The overall goal of this "Integrated Research Training Program of Excellence in Radiochemistry" is to provide a rich and deep research experience in state-of-the-art radiochemistry and in the fundamentals of radioisotopic labeling and tracer methodology to develop researchers who are capable of meeting the challenges of designing and preparing radiotracers of broad applicability for monitoring and imaging diverse biological systems and environmental processes. This program was based in the Departments of Radiology and Radiation Oncology at Washington University Medical School and the Department of Chemistry at the University of Illinois at Urbana Champaign, and it was initially directed by Professor Michael J. Welch as Principal Investigator. After his passing in 2012, the program was led by Professor Suzanne E. Lapi. Programmatic content and participant progress was overseen by an Internal Advisory Committee of senior investigators consisting of the PIs, Professor Mach from the Department of Radiology at Washington University and Professor John A. Katzenellenbogen of the Department of Chemistry at the University of Illinois. A small External Advisory Committee to give overall program guidance was also constituted of experts in radiolabeled compounds and in their applications in environmental and plant science.

The participants for this research program, a combination of graduate students and postdoctoral fellows, worked on a broad range of research projects in the diverse, fundamental components of radiochemistry: isotope production and purification, radiochemical synthesis, probe design and evaluation *in vitro*, in cells, and *in vivo*. The program participants also received formal coursework training in the fundamentals of isotope production, the synthesis of isotopically labeled compounds, and their use of isotopic analysis of physical and biological systems. Their research experience was supplemented and broadened by participation in seminar programs and scientific conferences on isotope chemistry and isotopic analysis, and through visits to laboratories of colleagues and collaborators involved in thematically relevant, complementary research.

In contrast to the relatively narrow range of experience provided by most of the current research and training programs in these areas, our program of integrated research-based training was carefully designed to provide a breadth and depth of experience sufficient to prepare a new generation of research scientists to become leaders in this field. Because they are superbly equipped to design and prepare isotopically labeled probe agents that will be effective for the quantitative and image-based analyses of materials flux and distribution needed to solve critical problems in biology and environmental sciences, they will maintain the vitality of this field and develop new programs of research and training needed to continue to address important problems for our Nation.

## Goals of the Research Training Program

- *Research Projects* that provided:
  - A deep experience in the fundamentals of design and synthesis of radioisotopically labeled compounds
  - An appreciation of diverse application areas that integrate aspects of the four priority research areas specified by the OBER DOE.
    1. Development of new chemical reactions that meet the demands and synthetic constraints of working with radioisotopes at high specific activity
    2. Use of physical chemistry to develop models predictive of chemical behavior at the tracer mass scale
    3. Construction of platforms with one or more imaging agents and targeting moieties
    4. Development of flexible automation technologies for radiotracer synthesis
- *Formal Coursework* requirements to broaden the experience of program participants in isotope production, stable and radioisotope synthesis, isotope probe design, and applications to problems, broadly, in biology and environmental studies.
- *Supplemental Experience* through regular *seminars*, participation in radiochemistry *scientific conferences* and *laboratory rotations/research visits* to other program faculty or collaborator laboratories to further enlarge the experience and vision of program participants.

## PERSONNEL SUMMARY

### Academic

Suzy Lapi: -10% June 2012-March 2013
Michael Welch: -10% February 2010-July 2010 and -5% August 2010-April 2012

### Staff

Kaavya Cherukuri -June 2013-May 2014 (Bi-weekly paid per hour)
Nora Goscinski - 100% August 2013-July 2014
Amrita Hari-Raj - September 2013-August 2014 (Bi-weekly paid per hour)
Kimberly Kania - 5% March 2011-January 2013 - 1% February 2013-March 2014
Chiedza Mupanomunda - June 2013-May 2014 (Bi-weekly paid per hour)
Michelle Wynn - 5% March 2011-February 2013
Alexander Zheleznyak - 25% September 2012-May 2014

### Graduate Students

Yunjun Guo - 100% October 2009-May 2012
Majiong Jiang - 100% July 2010-May 2011
Tara Mastren - 100% March 2014-August 2014
Xingyu Nie - 100% September 2012-July 2013
Xin Peng - 100% May 2010-August 2013

### Postdoc Research Associate

Tolulope Aweda - 50% December 2013-August 2014
Nilantha Bandara - 100% February 2012-August 2014
Ravindra De Silva - 100% October 2010-December 2011
Yunjun Guo - 50% June 2012-May 2013
Sandeep Jain - 100% December 2009-October 2010
Mai Lin - 100% November 2010-November 2012
Bernadette Marquez - 100% January 2012-August 2013
David Ranganathan - 100% November 2010-March 2012
Fei Xie - 100% April 2010-March 2011
Haiying Zhou - 100% April 2012-July 2013 - 50% August 2013-May 2014

### Postdoc Research Fellow (Stipend)

Bernadette Marquez - 75% September 2013-November 2013

## Trainees

Over the course of the program the following trainees were supported and worked on detailed projects related to this program. Additional undergraduate students were also supported and worked on small projects related to the program.

**Ravindra DeSilva**, a trainee who worked jointly with Drs. Suzanne Lapi and Buck Rogers, was involved in the production of Zr-89 which has both medical uses and applications in metal transportation in plants. He was also investigating the evaluation of new chelates for Cu-64 and Ga-68. His research involves the basic complex chemistry for radioactive metals, an area applicable to many applications of interest to DOE. Dr. Desilva is currently a radiochemist at Anschutz Medical campus, Department of Radiology University of Colorado Denver.

**Sandeep Jain** worked jointly with Drs. Suzanne Lapi and Buck Rogers on Zr-89 radiochemistry. Dr. Jain is now a staff member at a pharmaceutical company in India.

**Tara Mastren** was a graduate student supervised by Dr. Suzanne Lapi who worked on novel chemical separations with relevance in isotope production applications. Dr. Mastren received her PhD and is now a postdoctoral fellow at the University of Texas, Southwestern.

**Dexing Zeng** was a trainee mentored by Professor David Reichert and worked on the development of microfluidic devices for use in radiochemistry. Dr. Zeng is now a faculty member at the University of Pittsburgh in the department of Radiology.

**David Ranganathan** was a postdoctoral trainee mentored by Professor David Reichert. Dr. Ranganathan obtained his Ph.D. in analytical chemistry and was involved in the radiolabeling of biomolecules with Cu-64 and Ga-68 using microfluidic systems. Dr. Ranganathan is now a staff member at Radiomedix, a radiopharmaceutical company based in Texas.

**Haiying Zhou** was a postdoctoral fellow mentored by Professor David Reichert involved in performing radiochemistry on microfluidic devices.

**Mai Lin**, supervised by Professors Welch and Lapi, was involved in the implementation and evaluation of a Ge-68/Ga-68 generator in conjunction with an automated synthesis system supplied by Eckert & Ziegler. This work will allow the availability of Ga-68 labeled radiopharmaceuticals for many applications as well as allowing the trainee to obtain experience in the handling of these radiometals. Dr. Lin was also synthesizing peptides radiolabeled with radiometal nuclides using DOTA and NOTA as chelates. He was comparing the behavior of these two peptide chelate metal complexes labeled with Ga-68 and Cu-64. Dr. Lin is currently at staff scientist at MD Anderson.

**Xin Peng** was a graduate student trainee who received a Ph.D. degree in the Department of Chemistry working with Dr. Robert Mach. Although her project directly involves the development of selective $D_3$dopamine radiotracers, she has synthesized a compound library and screened this library to determine the most potent $D_3$ receptor tracer candidate. This training could be important in the evaluation of agents for many applications of importance to DOE. She also has labeled molecules with C-11 on the thiophenol position and developed a high-yield reaction.

**Yunjun Guo,** was a chemistry graduate student working with Dr. Carolyn Anderson. She has synthesized new crossbridge copper chelates and compared them with other chelates. This technology could have applications in many areas of science.
**Majiong Jiang,** was graduate student with Carolyn Anderson worked on the evaluation of crossbridge chelators. Dr. Jiang is now a postdoctoral fellow at UC Davis.

**Vincent Carroll** was a graduate student working in the Department of Chemistry at the University of Illinois under the supervision of John Katzenellenbogen. His thesis title was "*Approaches to labeled dendrimeric and other nanoparticles species with fluorine-18 using enhanced fluorosilane systems*." Working with other chemists in the Illinois laboratory, who have developed novel aryl silanes that can be labeled with fluorine more efficiently and under milder conditions. Vince spent time at Washington University to examine how several methods can be adapted to F-18 labeling. Currently there is a missing link in fluorine chemistry in the synthesis of F-18 labeled compounds which this technique addresses. The successful development of these methods could greatly widen the types of molecules that can be labeled with F-18 and have applications in many areas of science. Dr. Carroll is now a postdoctoral fellow at Molecular NeuroImaging.

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## Courses Developed and Training Opportunities

A new course, taught in the department of chemistry, "Radiochemistry for the Life Sciences", has been developed jointly by Professors Anderson and Lapi and taught by Dr. Lapi and several guest lecturers (including Professors Katzenellenbogen and Rogers). All trainees either took this course for credit or audited the course. It is planned that this course be taught every other year. The lectures form this course are all saved and available for viewing by the University of Illinois trainees.

All of the trainees obtained experience in the production of common cyclotron produced radionuclides and the radiolabeling of molecules. The trainees spend approximately 10% of their time viewing or carrying out these subprojects. As examples of the projects, Drs. Lin and DeSilva are involved in the synthesis of F-18 labeled hormones, Xin Peng in the development of routinely produced C-11 compounds and subprojects are being developed for the other trainees. The extra year of funding allowed the trainees to receive greater exposure to the cyclotron production and synthesis of radiopharmaceuticals and specifically allow the new trainees to become involved in this area.

Washington University is one of only a very few places in the country where these trainees have access to such broad and diverse training experience in radiochemistry. With the additional support to allow for our program to continue for a 4$^{th}$ year, we can provide a more complete training to our current trainees as well as to recruit additional trainees working on projects directly related to the DOE mission.

## Trainee Abstracts and Publications

Imaging EGFR expression in human cancer xenografts: Evaluation of panitumumab-NCS-DFO-Zr-89
De Silva, Ravindra A.; Chang, Albert J.; Lapi, Suzanne
JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS
Volume: 54 Supplement: 1 Pages: S370-S370 Published: 2011

Production and Purification of Silver-111
Lin Mai; Cutler, Cathy; Lapi, Suzanne
JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS
Volume: 54 Supplement: 1 Pages: S52-S52 Published: 2011

89Zr-Radiolabeled Trastuzumab Imaging in Orthotopic and Metastatic Breast Tumors.
Chang, Albert J; Desilva, Ravindra; Jain, Sandeep; et al.
Pharmaceuticals (Basel, Switzerland) Volume: 5 Issue: 1 Pages: 79-93 Published: 2012 Jan 05

Development and Characterization of Zr-89-Labeled Panitumumab for Immuno-Positron Emission Tomographic Imaging of the Epidermal Growth Factor Receptor
Chang, Albert J.; De Silva, Ravindra A.; Lapi, Suzanne E.
MOLECULAR IMAGING Volume: 12 Issue: 1 Pages: 1-+ Published: JAN-FEB 2013

Long-term evaluation of TiO 2-based 68Ge/ 68Ga generators and optimized automation of [ 68Ga]DOTATOC radiosynthesis
Mai Lin; Ranganathan, D.; Mori, T.; et al.
Applied Radiation and Isotopes Volume: 70 Issue: 10 Pages: 2539-44 Published: Oct. 2012

Microfluidic radiolabeling of biomolecules with PET radiometals
Zeng, Dexing; Desai, Amit V.; Ranganathan, David; et al.
NUCLEAR MEDICINE AND BIOLOGY Volume: 40 Issue: 1 Pages: 42-51 Published: JAN 2013

Multifunctional triazine-based molecules: A versatile platform for the application of targeted PET imaging probes
Li, Hairong; Zeng, Dexing; Reichert, David E.
ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY Volume: 244 Meeting Abstract: 18-NUCL Published: AUG 19 2012

Development of microfluidic based "click chemistry" via three different approaches
Ranganathan, David; Zeng Dexing; Reichert, David E.; et al.
JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS
Volume: 54 Supplement: 1 Pages: S47-S47 Published: 2011

Microfluidic labeling of biomolecules with radiometals for use in nuclear medicine
Wheeler, Tobias D.; Zeng, Dexing; Desai, Amit V.; et al.
LAB ON A CHIP Volume: 10 Issue: 24 Pages: 3387-3396 Published: 2010

Utilizing electrostatic interactions to facilitate F-18 radiolabeling of poly(amido)amine (PAMAM) dendrimers
Zhou, Dong; Kim, Sung Hoon; Carroll, Vincent M.; et al.
ORGANIC & BIOMOLECULAR CHEMISTRY Volume: 12 Issue: 43 Pages: 8696-8701 Published: 2014

Biodistribution studies with an F-18 labeled estrogen dendrimer conjugate ([F-18]EDC), which selectively stimulates extranuclear-initiated estrogen receptor action and affords selective cardiovascular protection, shows selective uptake and retention in cardiovascular tissues
Carroll, Vincent M.; Kim, Sung Hoon; Zhou Dong; et al.
JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS
Volume: 56 Supplement: 1 Pages: S30-S30 Meeting Abstract: O-030 Published: MAY 2013

Diarylpropionitrile (DPN) Enantiomers: Synthesis and Evaluation of Estrogen Receptor beta-Selective Ligands
Carroll, Vincent M.; Jeyakumar, M.; Carlson, Kathryn E.; et al.
JOURNAL OF MEDICINAL CHEMISTRY Volume: 55 Issue: 1 Pages: 528-537 Published: JAN 12 2012

Study of nucleophilicfluorination on electron-rich aromatic rings from non-aromatic precursors
Yasui, Norio; Carroll, Vincent M.; Katzenellenbogen, John A.; et al.
JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS
Volume: 54 Supplement: 1 Pages: S467-S467 Published: 2011

Exploring F-18 labeling of diaryiodonium salts: From model reactions to F-18 radiosynthesis of a peroxisome proliferator-activated receptor-gamma (PPAR-gamma) ligand
Zhou, Dong; Kim, Sung Hoon; Carroll, Vincent; et al.
JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS
Volume: 56 Supplement: 1 Pages: S164-S164 Meeting Abstract: P077 Published: MAY 2013

Silicon-fluoride functionalized small molecule hormones: Prospects for PET imaging of estrogen receptors with Si-F-18 labeled ligands
Kim, Sung Hoon; Carroll, Vincent M.; Katzenellenbogen, John A.; et al.
ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY Volume: 240 Meeting Abstract: 39-NUCL Published: AUG 22 2010

Estrogen-dendrimer conjugate labeled with fluorine-18 for PET imaging
Kim, Sung Hoon; Carroll, Vincent M.; Katzenellenbogen, John A.; et al.
ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY Volume: 240 Meeting Abstract: 40-NUCL Published: AUG 22 2010

Comparison of Conjugation Strategies of Cross-Bridged Macrocyclic Chelators with Cetuximab for Copper-64 Radiolabeling and PET Imaging of EGFR in Colorectal Tumor-Bearing Mice
Zeng, Dexing; Guo, Yunjun; White, Alexander G.; et al.
MOLECULAR PHARMACEUTICS Volume: 11 Issue: 11 Pages: 3980-3987 Published: NOV 2014

Roles of Atox1 and p53 in the trafficking of copper-64 to tumor cell nuclei: implications for cancer therapy
Beaino, Wissam; Guo, Yunjun; Chang, Albert J.; et al.
JOURNAL OF BIOLOGICAL INORGANIC CHEMISTRY Volume: 19 Issue: 3 Pages: 427-438 Published: MAR 2014

The Role of p53 in Combination Radioimmunotherapy with Cu-64-DOTA-Cetuximab and Cisplatin in a Mouse Model of Colorectal Cancer
Guo, Yunjun; Parry, Jesse J.; Laforest, Richard; et al.
JOURNAL OF NUCLEAR MEDICINE Volume: 54 Issue: 9 Pages: 1621-1629 Published: SEP 1 2013

Metal-free click chemistry with cross-bridged chelators to prepare Cu-64 labeled cetuximab in high specific activity for PET imaging of EGFR expression
Zeng Dexing; Guo Yunjun; Cai Zhengxin; et al.
JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS Volume: 56 Supplement: 1 Pages: S85-S85 Meeting Abstract: O-085 Published: MAY 2013

Preparation and Biological Evaluation of Cu-64 Labeled Tyr(3)-Octreotate Using a Phosphonic Acid-Based Cross-Bridged Macrocyclic Chelator
Guo, Yunjun; Ferdani, Riccardo; Anderson, Carolyn J.
BIOCONJUGATE CHEMISTRY Volume: 23 Issue: 7 Pages: 1470-1477 Published: JUL 2012

Strategies for improving specific activity and biodistribution of copper-64-labeled anti-EGFR antibody cetuximab
Anderson, Carolyn J.; Guo, Yunjun; Zeng, Dexing; et al.
ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY Volume: 243 Meeting Abstract: 13-NUCL Published: MAR 25 2012

Preparation and biological evaluation of Cu-64 labeled Tyr(3)-Octreotate using a phosphonic acid derivative of cross-bridge cyclam as the chelator
Guo, Yunjun; Ferdani, Riccardo; Anderson, Carolyn J.
JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS Volume: 54 Supplement: 1 Pages: S368-S368 Published: 2011

Synthesis, Cu(II) complexation, Cu-64-labeling and biological evaluation of CB-TE1A1P
Ferdani, Riccardo; Guo, Yunjun; Stigers, Dannon; et al.
NUCLEAR MEDICINE AND BIOLOGY Volume: 37 Issue: 6 Pages: 690-690 Published: AUG 2010

Relationship between cisplatin, copper-64 radiopharmaceuticals and p53 in the trafficking of Cu-64 to the nuclei of tumor cells
Guo, Yunjun; Zheleznyak, Alexander; Anderson, Carolyn J.
NUCLEAR MEDICINE AND BIOLOGY Volume: 37 Issue: 6 Pages: 706-706 Published: AUG 2010

Facile purification and click labeling with 2-[F-18]fluoroethyl azide using solid phase extraction cartridges
Zhou, Dong; Chu, Wenhua; Peng, Xin; et al.
TETRAHEDRON LETTERS Volume: 56 Issue: 7 Pages: 952-954 Published: FEB 11 2015

Synthesis, pharmacological evaluation and molecular modeling studies of triazole containing dopamine D-3 receptor ligands
Peng, Xin; Wang, Qi; Mishra, Yogesh; et al.
BIOORGANIC & MEDICINAL CHEMISTRY LETTERS Volume: 25 Issue: 3 Pages: 519-523 Published: FEB 1 2015

Synthesis and Structure-Activity Relationship Studies of Conformationally Flexible Tetrahydroisoquinolinyl Triazole Carboxamide and Triazole Substituted Benzamide Analogues as sigma(2) Receptor Ligands
Bai, Suping; Li, Shihong; Xu, Jinbin; et al.
JOURNAL OF MEDICINAL CHEMISTRY Volume: 57 Issue: 10 Pages: 4239-4251 Published: MAY 22 2014

Synthesis, [F-18] radiolabeling, and evaluation of poly (ADP-ribose) polymerase-1 (PARP-1) inhibitors for in vivo imaging of PARP-1 using positron emission tomography
Zhou, Dong; Chu, Wenhua; Xu, Jinbin; et al.
BIOORGANIC & MEDICINAL CHEMISTRY Volume: 22 Issue: 5 Pages: 1700-1707 Published: MAR 1 2014

Development of a fluorine-18 labeled isoxazole-based sigma-2 receptor ligand for PET imaging of cell proliferation
Peng Xin; Zhou Dong; Li Shihong; et al.
JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS Volume: 56 Supplement: 1 Pages: S382-S382 Meeting Abstract: P295 Published: MAY 2013