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*Designed and Produced by:*
Irene Christian  
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Director’s Report

The Center for Proteomics and Bioinformatics (CPB) 2012-2013 annual report highlights the structural and systems biology research of its faculty and staff. Over 43 Department and Divisions at the University used the Center’s facilities in the last year and the primary faculty, staff, and users published over 125 papers. The 14 secondary faculty, representing 10 departments, continued to make important strategic contributions to the research and education programs of the center. Also, Center for Synchrotron Biosciences (CSB) x-ray beamlines at Brookhaven laboratories, operated by CPB faculty and staff, served over 500 users from across the globe to conduct a range of structural biology research.

A major accomplishment this year includes the award of a $4 million grant over 5-years including funds from the National Science Foundation, the State of Ohio, and the University, to build a new structural biology beamline at the Department of Energy’s new synchrotron at Brookhaven. This new accelerator, the NSLS-II, will have the brightest and most intense x-ray beams in the world and the x-ray footprinting facility, called XFP, built by the CSB, will be one the first beamlines completed at the new facility. Using the intense x-ray beams of the NSLS-II, Case scientists, their collaborators, and guest users from across the world will have un-paralleled power to probe the structure and dynamic functions of membrane proteins like potassium channels and G-protein coupled receptors and better understand the action of important drugs. Nearly 40 user groups have already submitted proposals to use the facility when it opens in late 2015. The Center is also partnering with other structural biology teams at Brookhaven to develop leading crystallography facilities and to provide a unique integrated biophysics program where multiple techniques are routinely used to solve complex biomedical science projects. An example of such integrative approach can be found on pg. 6 in research carried out by a team including the Center and the Department of Pharmacology published in Proceedings of the National Academy of Sciences. The CSB beamlines and team, which have been built over a twenty year period, will in a year’s time have to close down operations at the existing NSLS facility, paving the way for the new ring and new and brighter science to come. Stay tuned for further developments!

Meanwhile, back in Cleveland, the faculty at the Center for Proteomics and Bioinformatics have been developing innovative education programs to enable students (and perhaps their mentors as well!) to join the “Big Data” revolution. The graduate program in Systems Biology and Bioinformatics, now starting its second full year has 12 students, and new tracks in Clinical Research Informatics and Applied Health Informatics (see pg. 7). An important goal of several new courses is to ready students for mining large electronic health records to understand and optimize patient outcomes. Flexible course times and hours, problem based learning, use of technology and modern media techniques are also standard fare for these new curricula.

Developing advanced approaches to analyze protein structure and signaling are also part of the daily efforts of center staff. Novel phosphorylation sites on CDK9 that signal immune activation in HIV infection were discovered and published in PLoS Pathogens (see pg. 5), but investigator needs to understand global signaling led the Center to launch global phosphoproteomics analysis including new bioinformatics tools, which are being piloted by groups from the Case Comprehensive Cancer Center and the Center for AIDS Research. Next year, we expect quite interesting results from these new studies and we look forward to telling you about them. Thanks for all of your support in the last year.

- Mark Chance
DNA and chromatin modification networks distinguish stem cell pluripotent ground states.

Pluripotent stem cells are capable of differentiating into all cell types of the body and therefore hold tremendous promise for regenerative medicine. Despite their widespread use in laboratories across the world, a detailed understanding of the molecular mechanisms that regulate the pluripotent state is currently lacking. Mouse embryonic (mESC) and epiblast (mEpiSC) stem cells are two closely related classes of pluripotent stem cells, derived from distinct embryonic tissues. Although both mESC and mEpiSC are pluripotent, these cell types show important differences in their properties suggesting distinct pluripotent ground states. To understand the molecular basis of pluripotency, we analyzed the nuclear proteomes of mESCs and mEpiSCs to identify protein networks that regulate their respective pluripotent states. Our study used label-free LC-MS/MS to identify and quantify 1597 proteins in embryonic and epiblast stem cell nuclei. Immunoblotting of a selected protein subset was used to confirm that key components of chromatin regulatory networks are differentially expressed in mESC and mEpiSC at p < 0.1 (Student’s t test).

Selected mESC- and mEpiSC-associated protein networks. Ingenuity Pathway Analysis (IPA) reveals differentially expressed subnetworks including (A) Polycomb-group (PcG), DNA methyltransferase, Nucleosome remodeling/histone deacetylase (NuRD), OCT4-SOX2-NANOG and SWI/SNF BAF complexes, B, Protein networks functioning in DNA replication and Genome surveillance/DNA repair, (C) Transcription factor complexes, and (D) Homeobox protein complex. All proteins shown were identified as being either more abundant in mESC (red nodes) or more abundant in mEpiSC (green nodes) at p < 0.1 (Student’s t test).
Ser175 phosphorylation of CDK9 is rapidly induced by T-cell activation signals.

(A) Affinity purification of FLAG-CDK9 complexes from Jurkat 2D10 cells and their identification by mass spectrometry. The percent values indicate the sequence coverage of the identified proteins. (B) Manually annotated MS/MS fragmentation spectra of the unmodified (upper) and phosphorylated (lower) CDK9 AFSLAK tryptic precursor peptides. (C) Ratio of phosphorylation of CDK9 at Ser175 and Thr186 in PMA stimulated (50 ng/ml) versus untreated cells with or without pretreatment with 20 µM U0126.

**Phosphorylation of CDK9 at Ser175 enhances HIV transcription and is a marker of activated P-TEFb in CD4(+) T lymphocytes.**

Mbonye UR, Gokulrangan G, Datt M, Dobrowolski C, Cooper M, Chance MR, Karn J.


The HIV transactivator protein, Tat, enhances HIV transcription by recruiting P-TEFb from the inactive 7SK snRNP complex and directing it to proviral elongation complexes. To test the hypothesis that T-cell receptor (TCR) signaling induces critical post-translational modifications leading to enhanced interactions between P-TEFb and Tat, we employed affinity purification-tandem mass spectrometry to analyze P-TEFb. TCR or phorbol ester (PMA) signaling strongly induced phosphorylation of the CDK9 kinase at Ser175. Molecular modeling studies based on the Tat/P-TEFb X-ray structure suggested that pSer175 strengthens the intermolecular interactions between CDK9 and Tat. Mutations in Ser175 confirm that this residue could mediate critical interactions with Tat and with the bromodomain protein BRD4. The S175A mutation reduced CDK9 interactions with Tat by an average of 1.7-fold, but also completely blocked CDK9 association with BRD4. The phosphomimetic S175D mutation modestly enhanced Tat association with CDK9 while causing a 2-fold disruption in BRD4 association with CDK9. Since BRD4 is unable to compete for binding to CDK9 carrying S175A, expression of CDK9 carrying the S175A mutation in latently infected cells resulted in a robust Tat-dependent reactivation of the provirus. Similarly, the stable knockdown of BRD4 led to a strong enhancement of proviral expression. Immunoprecipitation experiments show that CDK9 phosphorylated at Ser175 is excluded from the 7SK RNP complex. Immunofluorescence and flow cytometry studies carried out using a phospho-Ser175-specific antibody demonstrated that Ser175 phosphorylation occurs during TCR activation of primary resting memory CD4+ T cells together with upregulation of the Cyclin T1 regulatory subunit of P-TEFb, and Thr186 phosphorylation of CDK9. We conclude that the phosphorylation of CDK9 at Ser175 plays a critical role in altering the competitive binding of Tat and BRD4 to P-TEFb and provides an informative molecular marker for the identification of the transcriptionally active form of P-TEFb.
Beamline X3B and X29A: Structure of RPE65 isomerase in a lipidic matrix reveals roles for phospholipids and iron in catalysis.

Kiser PD, Farquhar ER, Shi W, Sui X, Chance MR, Palczewski K.


RPE65 is a key metalloenzyme responsible for maintaining visual function in vertebrates. Despite extensive research on this membrane-bound retinoid isomerase, fundamental questions regarding its enzymology remain unanswered. Here, we report the crystal structure of RPE65 in a membrane-like environment. These crystals, obtained from enzymatically active, nondelipidated protein, displayed an unusual packing arrangement wherein RPE65 is embedded in a lipid-detergent sheet. Structural differences between delipidated and nondelipidated RPE65 uncovered key residues involved in substrate uptake and processing. Complementary iron K-edge X-ray absorption spectroscopy data established that RPE65 as isolated contained a divalent iron center and demonstrated the presence of a tightly bound ligand consistent with a coordinated carboxylate group. These results support the hypothesis that the Lewis acidity of iron could be used to promote ester dissociation and generation of a carbocation intermediate required for retinoid isomerization.
Recent advances in technology and policy are driving a revolution in medicine and have spawned the new discipline of Biomedical Informatics, a hybrid science drawing upon fields as varied as bioinformatics, cognitive science, and epidemiology to advance the practice of clinical medicine. At its core, informatics in healthcare is concerned with the science of information and how health information can be collected, analyzed, and utilized to solve problems across the spectrum of clinical care. Research in biomedical informatics covers a broad range of topics, from projects on personalized genomic testing, to clinical decision support, to adverse drug reaction monitoring. The ubiquity and size of health-related datasets – whether coming from electronic medical records or from Twitter – has made the field of biomedical informatics indispensable to accountable care organizations, insurance companies, and healthcare systems needing to ensure that patients and providers are meeting health goals while controlling costs. As biomedical informatics operates at the nexus of a variety of disciplines, training in informatics similarly requires a multifaceted and interdisciplinary approach to introduce students to aspects of healthcare systems, databases, statistics, and decision science. Our new tracks will provide training to students to deal more effectively with problems that affect health systems on every scale – at the level of the molecule, the cell, the organ, the individual, and the population.

**Computational Molecular Biology**

To provide a home for the pursuit of basic science research in the SYBB program, the SYBB Track in Computational Molecular Biology will train students in the application and development of computational approaches to problems in molecular biology. From genome sequencing to protein folding, students will be equipped to analyze a wide variety of biological phenomena from the standpoint of systems biologist.

**Translational Bioinformatics**

Building on the combined strengths of the Department of Genetics and Genome Sciences and the Center for Proteomics and Bioinformatics, the new SYBB Track in Translational Bioinformatics will train students to work at the interface of -omics and clinical medicine. From integrating genomic data into EMRs, to developing tools to communicate genomic risk to consumers, students trained in Translational Bioinformatics will learn how bioinformatics tools and technologies can be integrated into clinical workflows. Graduates of this training track will find ample opportunities within industry and, as genomics enters the clinical arena, within hospitals, as well.

**Clinical Research Informatics**

The field of informatics and, accordingly, its training are divided into administrative informatics - entailing the installation, maintenance, and development of EMRs and other clinical databases - and research informatics - entailing the analysis of the data housed in such databases. Clinical Research Informatics is one of the primary domains in informatics that directly supports translational research. Consequently, MS-level training in this discipline can not only equip professionals to enter the biomedical workforce, but can also provide valuable instruction to medical students and physicians who wish to leverage informatics to improve their practice of medicine. The course of study in Clinical Research Informatics will guide students through the analysis of actual patient datasets provided by local hospitals, physicians, and/or companies. Instruction will be provided on topics ranging from informatics tools, to the structure of clinical databases, to the statistical analysis of clinical datasets, gradually teaching students how to work through real-world clinical scenarios to derive models, predictions, and insight that can improve the practice of medicine.

**Applied Health Informatics**

Specialists are also needed to handle the application of informatics and informatics technology to deliver healthcare services. To this end, the SYBB Track in Applied Health Informatics will train professionals in the operational and administrative aspects of informatics, including clinical decision support, clinical documentation, order entry systems, and system design and implementation. Designed to provide broad exposure to the overall field of informatics, as well as aspects of information systems management, students in this track will be trained to serve as informatics liaisons in clinical workflows or informatics administrators in industry.
Program Admission
Students can enter the SYBB program either through:
- Direct admission
- Biomedical Sciences Training Program (BSTP), http://www.case.edu/med/BSTP
- Medical Sciences Training Program (MSTP), http://mstp.case.edu

Direct Admission Process
Students can apply for direct admission to the SYBB program through the CWRU School of Graduate Studies online application (gradstudies.case.edu). The following items are needed to apply:
- Overall GPA, Science GPA
- GRE test scores
- TOEFL test scores (for international students only)
- Previous education and work experience
- 3 letters of recommendation
- Personal statement
- Research experience
- Scholastic and professional awards, fellowships, honors, and prizes
- Official transcript

Application Deadlines
Rolling admission

Program Competencies
The specific academic requirements of the SYBB program are intended to provide students with a core curriculum in Systems Biology and a set of electives designed both to assure proficiency in the three Fundamental Core Competencies and equip them for their particular thesis research discipline. Each trainee will be guided in a course of study by a mentoring committee to ensure the completion of training in the program competencies, along with the chosen track requirements.

Fundamental Core Competencies
- Genomics and Proteomics
- Bioinformatics and Biomedical Informatics
- Quantitative Analysis and Statistics

Ph.D. Program Summary
All Ph.D. students in the SYBB program will fulfill the overall academic requirements for Ph.D. study at Case Western Reserve University, including the requirement of 54 total credits including 12 pre-dissertation research credits, the candidacy examination, and a minimum of 18 dissertation research credits.

For example, the Translational Bioinformatics track includes a set of required core courses including:
- Bioinformatics for Systems Biology (SYBB 459)
- Current Proteomics (SYBB 555)
- Systems Biology Journal Club (SYBB 501)
- An individualized course of study that includes at least six additional courses
- A qualifier exam, a Ph.D. thesis

Master’s Degree Plan A Program Summary
- 21 semester hours of course work
- A minimum of 9 SYBB 651 thesis credit hours
- A prepared individual thesis with oral examination defense

Master’s Degree Plan B Program Summary
30 semester hours of course work
A written comprehensive examination or major project with report to be administered and evaluated by the SYBB Steering Committee

Participating Departments
The SYBB program includes faculty and coursework from multiple departments and across the CWRU campus.

- Biology
- Biomedical Engineering
- Cancer Center
- Center for Proteomics and Bioinformatics
- Electrical Engineering and Computer Science
- Epidemiology and Biostatistics
- Genetics
- Mathematics
- Neurosciences
- Physiology and Biophysics
- Pharmacology

Career Prospects
Students with a degree in Systems Biology and Bioinformatics can look forward to a collaborative career in a number of fields including:
- Academia
- Pharma/Industry
- Bioengineering
- Entrepreneurial endeavors and more!

Questions? Contact Us!
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Rob Ewing, Ph.D., Assistant Professor
Sayan Gupta, Ph.D., Instructor *
Janna Kiselar, Ph.D., Instructor
David Lodowski, Ph.D., Assistant Professor
Masaru Miyagi, Ph.D., Assistant Professor
Vishal N. Patel, M.D. Ph.D., Visiting Instructor
Joan Schenkel, M.S., Instructor
Wuxian Shi, Ph.D., Assistant Professor *
John “Chip” Tilton, M.D., Assistant Professor
Sichun Yang, Ph.D., Assistant Professor
Elizabeth Yohannes, Ph.D., Instructor

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Andreas Engel, Ph.D., Professor
Mahmoud Ghannoum, Ph.D., Associate Professor
Mehmet Koyuturk, Ph.D., Assistant Professor
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Guo-Qiang Zhang, Ph.D., Professor

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Sasa Bjelic, Ph.D.
Erik Farquhar, Ph.D. *
Wei Huang, Ph.D.
Rod Nibbe, Ph.D.
Krishna Ravikumar, Ph.D.
Jing Song, Ph.D.

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Pamela Lorene Clark
Mark Lucera
Sean Maxwell
Lindsay Stetson
Danica Wiredja
Yenan Zhu

Administrative Support
Irene Christian, B.S., Systems Administrator
Maita Diaz, B.A., Department Assistant
Sean Maxwell, M.S., Programmer Analyst

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Don Abel, Research Associate *
Giri Gokulrangan, Ph.D. Research Associate
Serguei Ilchenko, Ph.D., Research Associate
Parminder Kaur, Ph.D., Research Associate
Yu Liu, Ph.D., Research Associate
Daniela Schlatzer, Sr. Research Associate
Michael Sullivan, Sr. Research Associate *
Sara Tomechko, Ph.D., Research Associate
John Toomey, Research Associate *
Benlian Wang, Ph.D., Sr. Research Associate
Liwen Wang, Ph.D., Research Associate
Krishna Vukoti, Ph.D., Research Associate
Yajuan “Megan” Wang, Ph.D., Research Associate

Research Assistants
Rhijuta D'Mello, M.S. *
Aiman Haqqani, M.S.
Fred Hazlett, M.S.
Xiaolin Li, B.S.
Kat'y Lundberg, M.S.
Liping Ma, Ph.D.
Caroline Tabler, B.S.
Li Wang, B.S.

Student Research
Erin Armentrout (CWRU)
Douglas Brubaker (CWRU)
Nicole Chesnokov (Hathaway Brown High School)
Marie Ebner (CWRU)
Lauren Elkin (CWRU)
Joshua Jones (CWRU)
George C. Linderman (CWRU)
Stephanie Milne (CWRU)
Vishal Shah (Westlake High School)

* Indicates faculty and staff members located at the Case Center for Synchrotron Biosciences at the National Synchrotron Light Source, Brookhaven National Laboratory in Upton, NY.
Facilities

The Center has 10,000 sq. ft. of laboratory space on the 9th floor of the Bio-medical Research Building in the School of Medicine and has additional lab space and office space on the first floor of the Wood building. Our instruments include:

- Dionex Ultimate 3000 RSLC nano LC interfaced to a Fourier Transform
- LTQ mass spectrometer equipped with a 7T superconductive magnet with ppm resolution for top-down and bottom-up proteomics.
- Waters nanoACQUITY UPLC interfaced to a LTQ Orbitrap XL mass spectrometer with ETD capabilities.
- Waters nanoACQUITY UPLC interfaced to a LTQ Orbitrap Velos mass spectrometer.
- Dionex Ultimate 3000 RSLC nano LC system interfaced to a Thermo TSQ Quantum Ultra mass spectrometer.
- GE/Amersham 2-D gel DIGE system with robotic spot picking.
- Pro-TOF 2000 MALDI mass spectrometer, with attamole sensitivity and 5 ppm resolution.
- 2 Waters nanoACQUITY UPLC interfaced to Orbitrap Elite mass spectrometers.

Bioinformatics facilities include commercially available and in-house developed software to assist researchers with protein identification, determining protein dysregulation as a function of stimulation (disease, drug treatment, etc.), network analysis, structural elucidation and integrative -omics strategies. Initially, proteins are identified through the use of Matrix Science Mascot, or MassMatrix. Once identified, Rosetta Biosoftware Elucidator then tracks changes in protein expression as a function of their stimulation. These statistically relevant expression changes are then input into pathway prediction software, such as Ingenuity Pathways Analysis (IPA) or Metacore. Once networks are predicted there are many validation strategies available in-house such as: Single Reaction Monitoring, ELISA and Immunoblots.
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<th>Trainee</th>
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Total Training Grant Funding Since 2005 $1,336,000
Center for Synchrotron Biosciences

The Center for Synchrotron Biosciences (CSB) operates four beamlines (X3A, X3B, X28C, X29) at the National Synchrotron Light Source (NSLS) at Brookhaven National Laboratory in New York. These highly productive facilities are national resources dedicated to X-ray crystallography for protein structure determination, X-ray absorption spectroscopy (XAS) for examination of metalloprotein structure, and synchrotron X-ray footprinting (XF) technologies for examining macromolecular structure and dynamics. In addition to robust in-house research programs, the CSB provides training in the use of these beamline resources and also scientific and technical expertise to researchers from around the world.

What’s New at the CSB
The CSB has continued its intensive focus on a variety of ongoing research projects (in-house, collaborative and service projects) over the past year at its NSLS beamlines. The XAS program continues to experience high levels of productivity at beamline X3B, with our newly introduced XAS capabilities at beamline X3A receiving increasing usage from the NSLS user community. X29 continues its enviable track record of racking up PDB deposits, with 213 structure deposits in the past year (second in the world to BL17U at the Shanghai Synchrotron Radiation Facility). Finally the XF program at X28C is robust and growing, and the beamline personnel have made considerable strides in automating data collection to facilitate increasingly complex in vivo and rapid mixing footprinting experiments. With the impending permanent closure of NSLS in September 2014, the CSB has increasingly directed its effort towards the transition to the new National Synchrotron Light Source II (NSLS-II) facility currently in the final stages of construction.

Transition of the CSB to NSLS-II
The new NSLS-II facility, being constructed across the street from NSLS and scheduled for completion in 2015, will be a state-of-the-art, medium-energy electron storage ring (3 GeV) designed to deliver world-leading intensity and brightness >10,000 times brighter than the current NSLS), opening up new frontiers in scientific research. CSB staff members have been highly active in shaping the scientific direction of the new facility through involvement in beamline development proposals and a variety of workshops. Over the past year, efforts have been redoubled to identify venues for continuation of the CSB scientific program at NSLS-II and elsewhere.

In the X-ray footprinting program, CSB scientific and engineering staff have entered the second year of NSF MRI funding to design and construct the NSLS-II XFP beamline, which is expected to become operational in late 2015. Intensive design efforts are currently ongoing, including participation in working groups to define a common set of optical design parameters for many NSLS-II beamlines including XFP. To provide capacity during the transition, an effort was undertaken to characterize possible beamlines for XF at other US synchrotrons (see Research Highlight).

For XAS and MX, several partnerships are being further developed by the CSB to ensure user access. The MX program at X29, which is jointly operated by CSB and the Protein Crystallography Research Resource, will transition to the new NSLS-II beamlines FMX and AMX. FMX and AMX will provide world leading capabilities in microfocusing for challenging crystals and automation for high throughput, respectively, and the CSB will continue its productive collaboration with BNL scientists to operate these beamlines at NSLS-II. The CSB XAS program will initially exploit partnerships with the Stanford Synchrotron Radiation Lightsource and the new ISS beamline at NSLS-II to provide access to X-ray spectroscopy resources for the biological XAS user community.

Finally, the CSB is aggressively pursuing the development of an Integrated Biophysics Program for NSLS-II, which will facilitate studies of biological systems that integrate two or more synchrotron techniques, including XF, MX, XAS, and small angle X-ray scattering (SAXS).

Research Highlight: Synchrotron X-Ray Footprinting on Tour
CSB personnel explored the possibility of using various beamlines at the Advanced Light Source (ALS), Advanced Photon Source (APS), and Cornell High Energy Synchrotron Source (CHESS) to provide facilities for XF measurements during the 12-18 month period between closure of NSLS X28C in September 2014 and completion of NSLS-II XFP in late 2015. This effort produced performance characterization data for many beamlines that could be used for XF during the transition (figure at right), and more importantly, led to significant outreach and dissemination of the technology to new user communities (Bohon et al. J. Synch. Rad. 2013, in press). The successful ALS experiments led to formation of a collaboration with Dr. CorieRalston of the Physical Biosciences Division at Berkeley Lab, who has obtained funding to acquire needed apparatus for the ALS XF program. The partnership with ALS beamlines will provide a strong venue for XF science during the NSLS-II transition, and will expand access to the technique, particularly on the West Coast.
Center for Synchrotron Biosciences
Summary of Renewal Proposal (P30-EB-09998)

Objectives
- Design, build and operate world-class facilities for biophysics research at the new National Synchrotron Light Source-II (NSLS-II).
- Extend multi-institutional and multi-agency partnerships for transdisciplinary synchrotron research in footprinting (FP), crystallography (MX), x-ray spectroscopy (XAS), small-angle x-ray scattering (SAXS), and innovative computational biology.
- Encourage a Biology Village vision for NSLS-II.

Project Key Personnel
- Mark Chance, PhD, PI and Project Director.
- Mike Sullivan, Chief Beamline Engineer.
- Wuxian Shi, PhD, Concierge, Director, Crystallography Core C.
- Jen Bohon, PhD, Director Footprinting Core A.
- Erik Farquhar, PhD, Director, X-ray Spectroscopy Core B.
- Steve Almo, PhD, Einstein College of Medicine, Collaborator and Advisory Committee.
- Sarah Woodson, PhD, Johns Hopkins U, Collaborator and Advisory Committee.

Timeline of Project: Construction, Commissioning and Operations of Beamlines

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<td>Comm.</td>
<td>XFP Operations (through 2019)</td>
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NSLS-II Timeline
- NSLS Ops End
- NSLS-II Operations

Funding Timeline
- Current P30
- P30 Renewed Cycle (until 2019)

Legend
- Design
- Construction
- Commissioning
- NSLS-II Activities
- Funding Activities

Beamlines & Publications Since 2003

<table>
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<th>Publications 2003-Present</th>
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<td>XAS, ISS, BMM</td>
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<td></td>
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The existing and proposed beamlines of the CSB.
Notable Ten-Year Accomplishments: 2003-2013

- Constructed and operated X29 undulator beamline for x-ray crystallography in partnership with Brookhaven scientists: achieved status as #2 beamline worldwide for Protein Database deposits.
- X28C: Concurrent folding of 16S RNA and induced fit in 30S ribosome assembly observed (Nature, 2009)
- X28C: Water channels mediate signaling in G-protein receptors (Proc. Nat. Acad. Sci., 2009, see figure right).
  - X29: Structural basis for the rescue of stalled ribosomes identified (Science, 2012).
  - X29: Crystal structures provided insights into the Fanconi Anemia DNA repair pathway (Science, 2011).
- CSB: Supported > 200 projects funded by > 200 NIH grant programs; PIs published > 1000 papers.

Special Projects: 2014-2019

- Construct and commission XFP beamline as leading worldwide facility for radiolytic footprinting research at NSLS-II.
- Establish temporary user facilities at Stanford and Berkeley synchrotrons to minimize effects of NSLS “dark period” for footprinting and x-ray spectroscopy users.
- Partner with NSLS-II scientists and engineers to commission and provide user support for world-class crystallography (FMX/AMX) and x-ray spectroscopy facilities (ISS/XAS).
- Measure sites of water binding and dynamics in ion channels on microsecond timescales.
- Combine local (FP, MX) and global (SAXS) details of structure and dynamics of nuclear receptor function (see figure below).
Primary Faculty and Staff Publications (48)


Service Research:

**X3B Beamline: X-ray Absorption Spectroscopy (11)**

Callan P. Spectroscopic Studies of Model Compounds With Relevance to Nickel Superoxide Dismutase, Nitrile Hydratase and Copper Related Neurodegenerative Disorders [Ph.D.]: University of Nevada, Reno; 2012.


X3A Beamline: Crystallography (1)


X29A Beamline: Crystallography (64)


Clatterbuck Soper SF. Late steps in 30S ribosome assembly in vivo: Johns Hopkins University; 2013.

Posters / Invited Presentations (39 total)


Kaur, P., Structural Analysis of Biotherapeutics using MS. HUPO, Boston, MA. September 2012. (oral presentation)


Miyagi, M. Hydrogen Exchange Method to Probe the Chemical Properties of Histidine Imidazole Groups in Proteins Department of Biochemistry, Case Western Reserve University, Cleveland, Ohio, January 10, 2013. (oral presentation)


Schlatzer, D., Gokulrangan, G., Dhawan, N., Ma’ayan, A., Mahzar, S., Ohlmeyer, M., Chance, M.R., Narla, G. Quantitative Global Phosphoproteomics of a MAPK-AKT Dual Pathway Inhibitor Anti-Cancer Drug. OMSS April 2013 Columbus, OH. (oral presentation)

Shi, W., Crystallographic Studies of 54Q (HIV gp41-based Antigen). P01 Program Project Group Meeting-HIV Glycoprotein Based Vaccine Development, March 4, 2013


Tilton, J. CD4+ Memory Stem Cells (TSCM) are Productively and Latently Infected by CCR5- and CXCR4-Tropic HIV. Keystone Symposia. Immune Activation in HIV Infection: Basic Mechanisms and Clinical Implications (D2). Breckenridge, CO, USA. April 2013. (oral presentation)

Tilton, J. Viral outcomes following fusion with CD4+ T cell subsets. CWRU CFAR Scientific Retreat. Cleveland, OH, USA. January 2013. (oral presentation)

Tilton, J. Probing HIV infection of T cells with a combination reporter virus. Microbiology and Molecular Biology Departmental Retreat, CWRU. Cleveland, OH USA. September 2012. (oral presentation)

Tilton, J. HIV Replication and Pathogenesis: New insights from a multi-stage reporter virus system. Ohio State University Department of Microbiology Seminar, Ohio State University, Columbus, OH, USA. January 2013. (oral presentation)


Vukoti, K. Life-Long Global Protein Turnover in Model Organism C. elegans. Human Proteome Organization (HUPO) 11th World Congress, Boston, MA. September 10, 2012. (oral presentation)

Vukoti, K. Quantitative Proteome Turnover in C. elegans. 10th Annual Ohio Mass Spectrometry Symposium 2013, Columbus, OH. April 15, 2013. (oral presentation)


Yang, S. Computational Approaches to Interpreting SAXS Data of Protein-Protein Complexes. European Synchrotron Radiation Facility, Grenoble, France, Oct. 1, 2012. (oral presentation)

Yang, S. Experiment-driven Coarse-grained Simulations of Protein-Protein Assembly. American Physical Society, Baltimore, MD. March 19, 2013. (oral presentation)

Yang, S. Coarse-grained Simulations of Protein-Protein Assembly. Kavli Institute for Theoretical Physics China, Beijing, June 27, 2013. (oral presentation)

Yohannes, E. Proteomics and bioinformatics (Core B) progress. PO1 oral mucosal Immunity in Vulnerable HIV infected Populations; External Scientific Expert Committee, School of Dental Medicine, CWRU, Nov. 16, 2012. (oral presentation)
<table>
<thead>
<tr>
<th>Student</th>
<th>Project Title</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erin Armentrout</td>
<td>Signaling differences in the HIV envelope (Env) proteins between viruses from chronically infected patients compared to recently infected patients.</td>
<td>John Tilton, Ph.D.</td>
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<tr>
<td>Douglas Brubaker</td>
<td>Integrative -omics for Identifying Dysregulated Signaling Pathways</td>
<td>Gurkan Bebek, Ph.D.</td>
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<tr>
<td>Nicole Chesnokov*</td>
<td>The 15 second Race to Label: Tagging Angiotensin with DEPC.</td>
<td>Sara Tomechko, Ph.D.</td>
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<tr>
<td>*High School Student</td>
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<tr>
<td>Marie Ebner</td>
<td>Signaling differences in the HIV envelope (Env) proteins between viruses from chronically infected patients compared to recently infected patients.</td>
<td>John Tilton, Ph.D.</td>
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<tr>
<td>Lauren Elkin</td>
<td>Inferring patterns of infectious diseases spread from social media.</td>
<td>Gurkan Bebek, Ph.D.</td>
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<tr>
<td>(CWRU)</td>
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<tr>
<td>Joshua Jones</td>
<td>Development of a pipeline to detect population specific SNPs from next generation sequencing data.</td>
<td>Yu Liu, Ph.D.</td>
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<tr>
<td>(CWRU)</td>
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<tr>
<td>George C. Linderman</td>
<td>Microarray Gene Expression Data analysis and integration with interaction networks (Software Developed: BiC and MAGNET)</td>
<td>Gurkan Bebek, Ph.D.</td>
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<tr>
<td>(CWRU)</td>
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<tr>
<td>Stephanie Milne</td>
<td>Kinetics of CD4 and coreceptor expression in cryopreserved cells.</td>
<td>John Tilton, Ph.D.</td>
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<tr>
<td>Vishal Shah*</td>
<td>Advancing MAGNET: Microarray Gene Expression Data Analysis Tools (Software: MAGNET)</td>
<td>Gurkan Bebek, Ph.D.</td>
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<td>*High School Student</td>
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<tr>
<td>(Westlake High School)</td>
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<tr>
<td>Date</td>
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<tr>
<td>June 27, 2013</td>
<td>Jing Song (Case Western Reserve University)</td>
<td>Understanding oncoprotein networks in cancer cells using knock-in and knock-out AP-MS</td>
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<td>June 20, 2013</td>
<td>Mehmet Koyuturk (Case Western Reserve University)</td>
<td>Enhancing Genome-Wide Association Studies via Integrative Network Algorithms</td>
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<tr>
<td>May 23, 2013</td>
<td>Goutham Narla (Case Western Reserve University)</td>
<td>Therapeutic targeting of tumor suppressor genes for cancer treatment.</td>
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<tr>
<td>April 25, 2013</td>
<td>Tanja Kortemme (University of California San Francisco)</td>
<td>Molecular Design and Functional Specificity - from Proteins to Cells</td>
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<tr>
<td>April 18, 2013</td>
<td>Yu Liu (Case Western Reserve University)</td>
<td>Discovery of common sequences absent in the human reference genome using pooled samples from next generation sequencing.</td>
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<td>April 11, 2013</td>
<td>Youwei Zhang (Case Western Reserve University)</td>
<td>Cell Cycle Checkpoint Regulation and Cancer Therapy</td>
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<td>March 28, 2013</td>
<td>Analisa Difeo (Case Comprehensive Cancer Center, Case Western Reserve University)</td>
<td>Identification of functional miRNAs involved in ovarian cancer pathogenesis</td>
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<td>March 21, 2013</td>
<td>A. Ecrument Cicek (Case Western Reserve University)</td>
<td>ADEMA: An Algorithm to Determine Expected Metabolite Level Alterations Using Mutual Information</td>
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<tr>
<td>February 28, 2013</td>
<td>Asha Kallianpur (Genomic Medicine Institute, Cleveland Clinic Lerner Research Institute)</td>
<td>Iron, Mitochondria and HIV-associated Neurological Complications in the HAART era</td>
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<td>February 14, 2013</td>
<td>Krishnakumar Ravikumar (Case Western Reserve University)</td>
<td>Modeling domain cross-talk in a nuclear receptor RXR</td>
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<td>January 31, 2013</td>
<td>David Serre (Genomics Medicine Institute, Cleveland Clinic Lerner Research Foundation)</td>
<td>Whole Genome Sequencing of Field Isolates Provides Robust Characterization of Genetic Diversity in Plasmodium vivax</td>
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<td>December 13, 2012</td>
<td>Benlian Wang (Case Western Reserve University)</td>
<td>Identification of post-translational modifications of membrane protein by mass spectrometry</td>
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<td>December 6, 2012</td>
<td>Wenhui Wang (Case Western Reserve University)</td>
<td>Network Integration Methods to Uncover Novel Disease-Gene and Drug Target Associations</td>
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<td>November 15, 2012</td>
<td>Rob Ewing (Case Western Reserve University)</td>
<td>Experimental and Computational Discovery of Functional Protein Interaction Networks</td>
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<tr>
<td>November 1, 2012</td>
<td>Masaru Miyagi (Case Western Reserve University)</td>
<td>A New Tool for Structural Biology: Histidine Hydrogen Exchange Strategy</td>
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<tr>
<td>September 27, 2012</td>
<td>David Samuels (Vanderbilt University Medical Center)</td>
<td>The Systems Biology of Mitochondrial DNA Replication</td>
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<tr>
<td>August 23, 2012</td>
<td>Thomas LaFramboise (Case Western Reserve University)</td>
<td>An Overview of the Cancer Genome Atlas and Some Applications</td>
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<td>July 19, 2012</td>
<td>Krishna Vukoti (Case Western Reserve University)</td>
<td>“Global assessment of proteome turnover in C. elegans” and “Towards the goal to better understand the mechanism of serine protease catalysis”</td>
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<tr>
<td>July 1, 2012</td>
<td>Vassiliy Bavro (Birmingham University, UK)</td>
<td>Integrative structural approaches to study of ion-channers - dissecting the potassium channel gating mechanism</td>
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<tr>
<td>Date</td>
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<tr>
<td>Principal Investigator</td>
<td>Type of Grant</td>
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<tr>
<td>Chance, Mark</td>
<td>P30 CA-043703</td>
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<td>UL1 RR-024989</td>
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<td>P30 EB-009866</td>
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<td>Chance, Mark</td>
<td>R01 EB-009688</td>
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<td>Chance, Mark</td>
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<td>Chance, Mark and Boom, Henry</td>
<td>R01 - HL106798</td>
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<td>Chance, Mark and Barnholtz-Sloan, Jill</td>
<td>Skirball Foundations</td>
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<td>Cooper, Kevin</td>
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<td>Bohon, Jen</td>
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<td>Daneshgari, Firouz</td>
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<td>Dazard, Jean-Eudes</td>
<td>R01 CA-60593</td>
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<td>Dearborn, Dorr</td>
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<td>Ewing, Rob</td>
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<td>Harris, Michael</td>
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<td>Karn, Jonathan</td>
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<td>Imanishi,Yoshikazu</td>
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<td>Karn, Jonathan</td>
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<td>Koyuturk, Mehmet and Chance, Mark</td>
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<td>Lhatoo, Samden Dorjee</td>
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<td>Lamb, Bruce</td>
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<td>Lodowski, David</td>
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<td>Miyagi, Masaru</td>
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<td>Monnier, Vincent</td>
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<td>Nibbe, Rod and Chance, Mark</td>
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<td>Palczewski, Krzysztof</td>
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<td>Stark, George</td>
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<td>Shi, Wuxian</td>
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<td>Surewicz, Witold</td>
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<td>Tilton, John</td>
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<td>Yang, Sichun</td>
<td>W81XWH-11-1033</td>
<td>NIH</td>
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| Other Federal and Non-Federal Revenue | 2005 | 2013 |

<p>| Total Funding                        | $67,843,078 |</p>
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<tr>
<th>Principal Investigator</th>
<th>Type of Grant</th>
<th>Agency</th>
<th>Title</th>
<th>Start Date</th>
<th>End Date</th>
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<tr>
<td>Chance, Mark</td>
<td>P30 EB-009866- S1</td>
<td>NIH</td>
<td>Case Center for Synchrotron Biosciences- Supplement</td>
<td>2011</td>
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<tr>
<td>Chance, Mark</td>
<td>S10 RR-028927</td>
<td>NIH</td>
<td>Thermo Electron LTQ Orbitrap XL</td>
<td>2010</td>
<td>2012</td>
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<td>Chance, Mark and Weinberg, Aaron</td>
<td>CWRU Interdisciplinary Alliance</td>
<td>CWRU</td>
<td>Center for Excellence in Immunobiology</td>
<td>2010</td>
<td>2012</td>
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<td>Daneshgari, Firouz</td>
<td>P20-DK090871</td>
<td>NIH</td>
<td>Urological Complications of Obesity and Diabetes</td>
<td>2010</td>
<td>2012</td>
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<td>Drumm, Mitch</td>
<td>P30DK027651</td>
<td>NIH</td>
<td>Translational Research in Cystic Fybrosis</td>
<td>2012</td>
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<td>Karn, Jonathan</td>
<td>P30 AI-036219</td>
<td>NIH</td>
<td>Center for AIDS Research - Proteomics Core- Supplement</td>
<td>2011</td>
<td>2013</td>
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<td>Karn, Jonathan</td>
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<td>NIH</td>
<td>UC Center for Aid Research</td>
<td>2012</td>
<td>2013</td>
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<td>Qu, Cheng-Kui</td>
<td>R01 HI-068212</td>
<td>NIH</td>
<td>Protein Tyrosine Phosphatases and Hematopoietic Cell Regulation</td>
<td>2007</td>
<td>2012</td>
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<td>Wintrobe, Patrick</td>
<td>R01 HL-085469</td>
<td>NIH</td>
<td>Molecular Basis of Serpin Function and Disfunction</td>
<td>2007</td>
<td>2012</td>
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<td>Xu, Hua</td>
<td>R21GM099028</td>
<td>NIH</td>
<td>UV Photodissociation for Acidic and Basic Proteome Characterization- Subcontract</td>
<td>2011</td>
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<tr>
<td><strong>Total Completed Project Funding Since 2005</strong></td>
<td><strong>$39,000,355</strong></td>
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## Recently Completed Projects

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<thead>
<tr>
<th>Recipient</th>
<th>Project</th>
<th>Year</th>
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<tr>
<td>Subauste, Carlos, MD</td>
<td>Identification of inhibitors of CD40 Signaling</td>
<td>2013</td>
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<tr>
<td>Anthony, Donald, MD, PhD</td>
<td>Role of ENPP2 and LGALS3BP in immune activation during HCV, HIV and HCV-HIV infection</td>
<td>2013</td>
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<tr>
<td>Medof, Edward MD, PhD</td>
<td>Evidence for a plasma membrane complex containing C5a receptor (C5aR), IL-6-receptor (IL-6R), and vascular endothelial cell growth factor receptor-2 (VEGFR-2) that governs vascular endothelial cell (EC) viability and growth signaling</td>
<td>2013</td>
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<tr>
<td>Stein, Catherine</td>
<td>Exploration of pathways underlying resistance to M. tuberculosis infection</td>
<td>2013</td>
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<tr>
<td>Chen, Shu PhD</td>
<td>Identification of novel substrates of LRRK2, a Parkinson disease associated kinase</td>
<td>2013</td>
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<tr>
<td>Wang, Liwen PhD</td>
<td>HIV-1 Antigen</td>
<td>2013</td>
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