BIOGRAPHICAL SKETCH

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NAME: Rebecca Page

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

POSITION TITLE: Professor of Cell Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Arizona, Tucson, Arizona	B.S.	05/1993	Biochemistry
University of Arizona, Tucson, Arizona	B.S.	05/1993	Applied Mathematics
Princeton University, Princeton, NJ	Ph.D.	01/2000	Chemistry/X-ray Cryst.
The Scripps Research Institute, La Jolla, CA	Post-doc	03/2003	Molecular Biology, X-ray Crystallography

A. Personal Statement

My group has a long-standing interest in signaling pathways regulating cell proliferation/differentiation and their derangement in human diseases. **A major focus of my work is the role of ser/thr phosphoprotein phosphatases (PPPs) in these pathways,** with a long-term goal of elucidating how PPPs dephosphorylate thousands of different protein substrates while allowing the level of phosphorylation to be individually and exquisitely regulated. The goal of this proposal is to elucidate how the nuclear specific PPP holoenzymes PP1 and PP2A-B55 control mitosis, especially mitotic exit, and, in turn, understand their role in cancer. To achieve this, my group integrates structural, biophysical, biochemical and cell biological methods to understand how PPPs, and their interaction with both regulatory proteins and substrates, drive signaling in cells. **We have made fundamental contributions to this field**: (1) revealing the PP1 regulatory code used by PP1-specific regulators to bind and direct the activity of PP1, (2) the discovery of the LxVP SLiM binding site on CN which showed that immunosuppressants bind CN at the LxVP site and thus inhibit CN activity by blocking its ability to bind substrates; (3) the discovery that the B-subunits of PP2A engage regulators and substrates using a phosphorylation-specific SLiM; among many others. These data are transforming our understanding of the highly specific and exquisitely regulated function of PPPs in biological signaling and disease.

Dr. Peti and I are long-term collaborators, having already co-authored scores of papers focused on elucidating the structural and functional basis of PPP regulation in cells and the cell cycle, with additional manuscripts in preparation. Further, I am a long-time collaborator with Dr. Kettenbach (we have co-authored six manuscripts including work to define CN substratomes using our structure-based shape complementarity SBSC method) and, more recently and Dr. Grana (one co-authored manuscript with a second in preparation). I have been funded since 2008 from the NIH, NSF (including a CAREER award), ACS (Research Scholar) among others. I have published 130 papers, many in high impact journals. My broad background in signaling and biophysics enables me to productively collaborate on the experiments outlined in this proposal, for which structure determination by crystallography is a key component. Throughout my tenure as a faculty member at Brown University, the University of Arizona and now at the University of Connecticut Health Sciences Center, I have directly mentored dozens of post-doctoral scientists, graduate students and undergraduates with alumni from my group having obtained highly competitive positions (senior crystallographer at Bristol-Myers Squibb; MIT/HHMI postdoctoral position as a Jane Coffin Childs Scholar who now has her own faculty position and laboratory at Vanderbilt University; postdoctoral position at Harvard, among others; 2 of my 6 graduate students received awards for the best dissertation either at the school, Brown University, or departmental, MCB Brown University, level). The research environment at my current institution (University of Connecticut Health Center, Cell Biology, School of Medicine) is exceptional, allowing my group, almost all of whom moved with me, to thrive both academically and

scientifically. Clearly, my training, my grant management skills, as well as my research, especially in the fields of phosphatases and signaling, demonstrate that I am highly qualified to contribute to the exciting, transformative studies outlined in this proposal.

Ongoing and recently completed projects include:

NX012-107-160-002
Page (PI)
01/03/2019 – 07/31/2022
Biophysical analysis of Novel Allosteric SHP2 Inhibitors

1R01GM098482
Page (PI)
NIH - NIGMS
09/01/2011 – 12/31/2020
The regulation of PP1 in the nucleus

1R01NS091336
Page (MPI)
02/01/2015 – 12/31/2020
Serine/Threonine Phosphatases in Neurological Diseases

NSF (MCB-1817621)
Page (MPI)
08/01/2018 – 12/31/2020
Understanding the molecular determinants and regulation of toxin activity in bacteria.

B. Positions and Honors

Academic Appointments

12/2020 – present	Professor, Department of Cell Biology, School of Medicine, University of Connecticut Health Center, Farmington, CT
7/2019 – 6/2020	CBC Associate Department Head of Academic and Faculty Affairs, *Interim*, University of Arizona, Tucson, Arizona
1/2019 – 12/2020	Professor, Department of Immunobiology, University of Arizona, Tucson, Arizona
1/2017 – 12/2020	Professor and Donna B. Cosulich Faculty Chair, Departments of Medicine and Chemistry & Biochemistry, University of Arizona, Tucson, Arizona
7/2015 – 12/2016	Professor of Biology, Molecular Biology, Cell Biology and Biochemistry, Brown University, Providence, RI
7/2011 – 6/2015	Associate Professor of Biology, (Tenured), Molecular Biology, Cell Biology and Biochemistry, Brown University, Providence, RI
7/2005 – 6/2011	Assistant Professor of Biology (Tenure-track), Molecular Biology, Cell Biology and Biochemistry, Brown University, Providence, RI
9/2004 – 6/2005	Assistant Professor of Medicine (Research), Molecular Pharmacology, Physiology and Biotechnology, Brown University, Providence, RI
4/2003 – 8/2004	Core Director, Crystallomics Core, Joint Center for Structural Genomics at The Scripps Research Institute, La Jolla, CA

Honors and Awards

6/2021	Keynote speaker, PDB50 sessions of the 2021 ACS National Meeting
2017 – 2020	Donna B. Cosulich Faculty Fellow, University of Arizona
2019	UBRP mentor of the year finalist, University of Arizona
2013	Eighteenth Annual Gehrenbeck Lecturer, Rhode Island College
2010 – 2015	NSF-CAREER award
2008	Hazeltine Citation Nominee (Brown University senior class teaching award)
2008 – 2011	American Cancer Society (ACS) Research Scholar
2005	Richard B. Salomon Faculty Research Award
2000 – 2003	Ruth L. Kirschstein National Research Service Award (NRSA), NIH
1997 – 1998	Harold W. Dodds Honorific Graduate Fellowship
1994 – 1997	National Science Foundation Graduate Fellowship

1993	Phi Beta Kappa
1992 – 1993	Barry M. Goldwater Undergraduate Research Scholar
1988 – 1992	Regents Academic Achievement Scholarship

Other Experience

Editorial

1/2017 – present	Associate Editor, *Science Advances*
7/2012 – present	Editorial Board Member, *Journal of Biological Chemistry*
2005 – 2017	Associate Editor, *Protein Expression and Purification*
2003 – present	*Reviewer for:* Nature Chemical Biology, Nature Communications, Nature Methods, Nature Structural & Molecular Biology, Science Signaling, eLife, PLoS Pathogens, Acta Cryst D/F, Biochem, J Biol Chem, FASEB J, J Mol Biol, Mol Cell Bioc, Mol Microbiol, Prot Exp Purif, Proteins: Struc Func Bioinformatics, Protein Science, *among others*

Study Sections/Reviewer

07/2016-09/2020	NIH MSFB (Macromolecular Structure and Function), *permanent member*
6/2016 – 5/2019	BNL National Synchrotron Light Source II scientific proposal review panel, *standing member*
7/2015	NIH ZRG1 BCMB-X (40) P01 review panel, *Ad hoc study section member*
7/2015	NIH ZRG1 BCMB-W (40) P41 *Ad hoc reverse site visit study section member*
2/2015	NIH NIGMS P41 pre-proposal (X02) review panel, *Ad hoc study section member*
2014 – 2016	Structural Biology Proposal Study Panel (PSP), ALS, LBNL, *Standing reviewer*
11/2013	NIH – MSFC (Macromolecular Structure and Function), *Ad hoc panel member*
7/2012	NIH – NCRR, ZRG1 BCMB P41 *Ad hoc site visit study section member*
10/2010	NSF – MCB, Cellular Systems Cluster, Cellular Homeostasis and Signaling Ad Hoc review panel member
10/2010	Temporary Member, NIH, NCI Innovative Molecular Analysis Technologies Program
3/2010	Temporary Member, NIH, NCI Innovative Molecular Analysis Technologies Program
2010	The Welcome Trust, Scientific Grant Reviewer
2009	Cancer Research UK, Project Grant Application Reviewer
2009	NSF Reviewer, Molecular Biochemistry Program
2007	Cancer Research UK, Project Grant Application Reviewer

Meeting Organizer/session chair

2017	Session Chair, Bacterial communities and mechanisms of microbial cell regulation, Session of the 2017 American Society of Biochemistry and Molecular Biology (ASBMB) meeting; Chicago, Il
2016	Co-organizer, Protein Structure Dynamics and Function: Sailing the Protein Seas, Providence, RI
2013	Session Chair, Structural Enzymology (I) Session of the 2013 American Crystallographic Association Meeting.
8/30/2008	Session Chair, Focused Structural Proteomics Microsymposium, XXI congress and General Assembly of the International Union of Crystallography, Osaka, Japan.
2/10/2008	Session Chair, Protein Expression Research Group Session, Association for Biomolecular Resource Facilities Annual Meeting, Salt Lake City, Utah, USA.

C. Contributions to Science: Total publications: 130; see
https://www.ncbi.nlm.nih.gov/myncbi/rebecca.page.1/bibliography/public/

(i) Mechanism of action and function of the ser/thr phosphoprotein phosphatase PP1. PP1, the best-characterized PPP, is regulated by its interaction with more than 200 known *targeting and inhibitor* proteins. This large diversity of binding partners is consistent with PP1's regulatory role in multiple cellular processes. Thus, specific PP1 inhibitors or activators hold enormous clinical potential for the treatment of a large variety of diseases. During the last 20 years, we have made substantial contributions to this field that are now leading to paradigm shifts in our understanding of PP1 regulation in the cells. First, our group has determined more structures of *PP1 holoenzymes* than any laboratory in the world. In 2007, only two PP1 holoenzyme structures, of the more than 200 PP1 holoenzymes that exist in the cell, had been determined. This dearth of structural information was due primarily to the exceptional difficulties of studying PP1 in the laboratory. Through a dedicated effort over multiple years, we overcame these challenges. Second, since 2010, we have determined

the structures of multiple PP1 holoenzymes as well additional natural toxin:PP1 complexes. Third, our structures have enabled us to identify completely novel interaction sites leading to the discovery of more than 10 distinct PP1 specific SLiMs. These are key advances for understanding the regulation of PP1. Fourth, we have also advanced the field of protein science in general. This is because most PP1 regulatory proteins are IDPs. This system is unique because it allows us to understand how a family of IDPs bind and interact with a single target, PP1. This is an exciting and growing field as more than 30% of all human proteins are predicted to have large IDP domains. Here, we are leveraging these discoveries to develop novel tools—PhosTAPs and PhosTACs—to identify all residues directly regulated by PP1 and to manipulate target phosphorylation levels, respectively.

(***1***). Choy, M.S., Swingle, M., D'Arcy, B., Abney, K., Rusin, S.F., Kettenbach, A.N., Page, R., Honkanen, R.E., Peti, W. (2017) PP1:Tautomycetin Complex Reveals a Path toward the Development of PP1-Specific Inhibitors. ***JACS***, 139: 17703-17706. PMID: 29156132
(***2***) Kumar, GS, Choy, MS, Koveal, DM, Lorinsky, MK, Lyons, SP, Kettenbach, AN, Page, R, Peti, W. (2018) Identification of the substrate recruitment mechanism of the muscle glycogen protein phosphatase 1 holoenzyme. ***Science Advances***, 4: 11. 11. PMID: 30443599.
(***3***). Betran, M.T., Mouelleron, S. Zhou, Y., Bajaj, R., Uliana, F., Kumar, G.S., van Drogen, A., Lee, R., Benerjee, J.J., Hauri, S., O'Reilly, N., Gstaiger, M., Page, R., Peti, W., Tapon, N. (2019) ASPP proteins discriminate between PP1 catalytic subunits through their SH3 domain and the PP1 C-tail. ***Nature Communications***. 10(1): 1-19. PMID: 30770806.
(***4***) Choy, M.S., Moon, T.M., Ravindran, R., Bray, J.A., Robinson, L.C., Archuleta, T.L., Shi, W., Peti, W., Tatchell, K. Page, R. (2019) SDS22 selectively recognizes and traps metal-deficient inactive PP1. ***PNAS*** 116: 20472-20481. PMID: 31548429.

(i) Mechanism of action and function of the ser/thr phosphoprotein phosphatase PP2A. PP2A is a ser/thr phosphatase that is essential for mitosis and cancer. Different from PP1, it forms trimeric holoenzymes that differ in the nature of the 'B' subunit (substrate specifying subunit). While it was thought for decades that SLiM-based regulator binding was restricted to PP1, we and others showed that CN and also PP2A:B56 use PPP-specific SLiMs to bind their cognate substrates/regulators, strongly suggesting that this SLiM-based mechanism is conserved throughout the entire family. Specifically, we showed that CN binds its substrates using the LxVP SLiM (in addition to the PxIxIT SLiM) and, further, that the LxVP binding site on CN is *exactly where the potent, blockbuster immunosuppressants cyclosporin A and FK506 bind.* We also demonstrated that PP2A:B56 binds specifically to LSPIxE motifs and discovered that this binding is *enhanced* by SLiM phosphorylation (in contrast, phosphorylation of PP1 SLiMs *inhibits* binding), leading to a 'timing mechanism' for PPP activity during mitosis which is regulated by phosphorylation. We also showed that SLiM binding is modulated by dynamic charge-charge interactions, events we expect will be particularly important for other PPP SLiM interactions. We our now focused on identifying the remaining PPP specific SLiMs, especially those for PP2A:B55 (this proposal), with our most recent discovery being the SLiM specific for PP2A:B55.

(***1***) Grigoriu, S., Bond, R., Cossio, P., Chen, J.A., Ly, N., Hummer, Page, R., Cyert, M.S., Peti, W. (2013) The molecular mechanism of substrate engagement and immunosuppressant inhibition of Calcineurin. ***PLoS Biology***, 11(2): e1001492; PMID: 23468591.
(***2***) Hendus-Altenburger, R. Wang, X., Sjogaard-Frich, LM, Pedraz-Cuesta, E. Sheftic, S.R., Bendsoe, A.H., Page, R., Kragelund, B.B., Pedersen, S.F., Peti, W. (2019) Molecular basis for the binding and selective dephosphorylation of Na/H exchanger 1 by calcineurin. ***Nature Communications***, 10: 1.08. PMID: 31375679
(***3***) Wang, X., Garvanska, D.H., Nasa, I., Ueki, Y., Zhang, G., Kettenbach, A.N., Peti, W., Nilsson, J., Page, R. (2020) A dynamic charge-charge interaction modulates PP2A: B56 substrate recruitment. ***eLife:*** 9: e55966. PMID 32195664.
(***4***) Fowle, F., Zhao, Z., Xu, Q., Wasserman, J.S., Wang, X., Adeyemi, M. Feiser, F., Kureimchak, A.N., Atar, D., McEwan, B.C., Kettenbach, A.N., Page, R., Peti, W., Dunbrack, R.L., Grana, X. (2021) PP2A/B55α substrate recruitment as defined by the retinoblastoma-related protein p107. ***eLife***, 10: e63181. PMID: 34661528.

(ii) The regulation of tyr phosphatases by regulatory proteins. The tyrosine phosphatases (HePTP, PTP1B) function to transduce environmental and developmental signals (growth factors, stress) into adaptive and programmed responses (differentiation, inflammation, apoptosis). We have used an integrated biophysical approach—employing NMR spectroscopy, X-ray crystallography and SAXS—in order to understand how these key signaling PTPs are regulated by their multiple interacting partners. Our work has led to the first structure of the MAPK:PTP complex (p38:HePTP), the structures of an activate and resting state MAPK:PTP complex (ppERK2:HePTP and ERK2:HePTP), and the discovery of new HePTP inhibitors. This work was funded by an

American Cancer Society Research Scholar award (RSG-08-067-01-LIB) and is described in >20 publications. Additionally, we have discovered how PTP1B activity is regulated by dynamics and conformation.

(***1***) Francis, D., Koveal, D., Rozycki, B., Hummer, G., Page, R.* & Peti, W.* (2011) Structural basis of p38α regulation by hematopoietic tyrosine phosphatase, ***Nature Chemical Biology***, 7, 916-924. PMCID: PMC3657131; *co-corresponding authors.
(***2***) Choy, M.S., Li, Y., Machado, L.E.S.F., Kunze, M.B.A., Connors, C., Wei, X., Lindorff-Larsen. K., Page, R., Peti, W. (2017) Conformational Rigidity and Protein Dynamics at Distinct Timescales Regulate PTP1B Activity and Allostery. ***Molecular Cell*** 65: 644-658. PMCID: PMC5325675.
(***3***) Kumar, GS, Clarkson, MW, Kunze, MBA, Granata, D, Wand, AJ, Lindorff-Larsen, K, Page, R, Peti, W. (2019) Dynamic activation and regulation of the mitogen-activated protein kinase p38. ***PNAS***. 115: 4655-4660. PMCID: PMC5939092.
(***4***) Torgeson, KR, Clakson, MW, Kumar, GS, Page, R, Peti, W. (2020) Cooperative dynamics across distinct structural elements regulate PTP1B activity. ***J. Biol. Chem.*** 295: 13829-13837. PMCID: PMC7535920.

(iii) Toxin-antitoxin systems and their role in biofilm formation and antibiotic resistance. Toxin:antitoxin (TA) systems are two component systems that encode a stable protein 'toxin' whose activity leads to growth arrest and an unstable protein 'antitoxin' or 'antidote' that binds the toxin and mitigates its toxicity. However, persistence and the role of TA systems in initiating the persister state, is one of the most poorly understood mechanisms used by bacteria to survive environmental stress. My group has made major scientific contributions to these questions. First, we showed that the gene most highly up-regulated in persister cells and which acts as a master regulator of biofilm formation, mqsR, is a bacterial toxin that, with its highly unique antitoxin, mqsA, defines an entirely new subfamily of type II toxin:antitoxin systems. Second, we discovered a novel family of TA systems, the Type V system, in which the antitoxin, GhoS, functions as an endoribonuclease that inhibits its cognate toxin, GhoT, by specifically cleaving its mRNA and preventing its translation. Third, we demonstrated that MqsRA TA system directly regulates the GhoTS TA system, and thus is the first TA system shown to directly regulate a second. Together, our work demonstrates that MqsRA defines an entirely novel family of Type II TA systems which has critical implications for understanding how TA systems regulate persistence, antibiotic resistance and biofilm formation in bacteria. These results have been communicated in 18 publications.

(***1***) Brown, B.L., Grigoriu, S., Kim, Y., Arruda, J.M., Davenport, A., Wood, T.K., Peti, W., Page, R. (2009). Three dimensional structure of the MqsR:MqsA complex: a novel TA pair comprised of a toxin homologous to RelE and an antitoxin with unique properties. ***PLoS Pathogens*** 5(12): e1000706; PMCID: PMC2791442.
(***2***) Wang, X., Kim, Y., Hong, S.H., Ma, Q., Brown, B.L., Pu, M., Tarone, A.M., Benedik, M.J., Peti, W., Page, R., and Wood, T.K. (2011). Antitoxin MqsA helps mediate the bacterial general stress response, ***Nature Chemical Biology***, 7, 359-366; PMCID: PMC3097263.
(***3***) Wang, X., Lord, D.M., Cheng, H-Y, Osbourne, D.O., Hong, S.H., Sanchez-Torres, V., Quiroga, C., Zheng, K., Hermann, T., Peti, W. Benedik, M.J., Page, R.,* Wood, T.K.* (2012) A New Type V toxin-antitoxin system where mRNA for toxin GhoT is cleaved by antitoxin GhoS, ***Nature Chemical Biology***, 8, 855-861; PMCID: PMC3514572. *co-corresponding authors.
(***4***) Page, R., Peti, W. (2016) Toxin:antitoxins systems in bacterial growth arrest and persistence. ***Nature Chemical Biology***, 12: 208-214. PMID: 26991085

(iv) Advances in structural biology. I made key discoveries to advance structural biology methods.
(***1***) Page, R., Grzechnik, S. K., Canaves, J. M., Spraggon, G., Kreusch, A., Kuhn, P., Stevens, R. C. & Lesley, S. A. (2003). Shotgun crystallization strategy for structural genomics: an optimized two-tiered crystallization screen against the *Thermotoga maritima* proteome. ***Acta Crystallogr D*** 59, 1028-1037. PMID: 12777766
(***2***) Canaves, J., Page, R., Wilson, I. A. & Stevens, R. C. (2004) Protein biophysical properties that correlate with crystallization success in *Thermotoga maritima*: maximum clustering strategy for structural genomics. ***J Mol Biol***, 344, 977-991. PMID: 15544807
(***3***) Page, R.*, Peti, W.*, Wilson, I. A., Stevens, R. C., & Wüthrich, K. (2005). NMR screening and crystal quality of bacterial expressed prokaryotic and eukaryotic proteins in a structural genomics pipeline. ***PNAS***, 102, 1901-1905. *equal contributions; PMCID: PMC548552.
(***4***) Collins, B., Stevens, R.C., Page, R. (2005) High-Throughput Optimum Solubility Screening: Using Crystallization Results to Identify the Optimal Buffer for Protein Crystal Formation. ***Acta Crystallogr F***, 61, 1035-1038; PMCID:PMC1978149.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Wolfgang Peti

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

POSITION TITLE: Professor of Molecular Biology & Biophysics; Department Chair

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Vienna, Vienna, Austria	Mag. *rer. nat.*	1/1997	Chemistry
Johann-Wolfgang-Goethe University, Frankfurt, Germany	PhD	9/2001	Chemistry, NMR
The Scripps Research Institute, La Jolla, Ca	Postdoc	08/2004	Structural Biology

A. Personal Statement

I have a long-standing interest in protein structure and function. I have been continuously funded by the NIH since 2006 and I have demonstrated broad expertise in structural biology, molecular biology, biochemical and biophysical techniques, as well as cell biology. As a graduate student in Christian Griesinger's laboratory, I pursued the development of novel NMR techniques for the analysis of protein dynamics. As a post-doc in Kurt Wüthrich's laboratory, I used NMR spectroscopy to study the structures and dynamics of proteins in distinct metabolic and signaling pathways in *T. maritima*, and in parallel developed new methods to determine structures with less material, less time and with a higher success rate. I was able to publish 36 peer-reviewed publications as a PhD and postdoctoral researcher.

I began my independent research career at Brown University in 2004. Here, I embarked on a completely novel research area, which involved both structural biology and molecular signaling research. I initiated investigations of protein phosphatases, kinases and bacterial signaling. Signaling pathways control life and the lack or interruption of the tight regulation that controls these pathways leads to disease. Over the last 18 years, I have made significant advances in our understanding of the regulation of enzymes that regulate signaling pathways via phosphorylation, the most dominant posttranslational modification. I left Brown to rebuild the University of Arizona (UA) biochemistry department. In 2020, I relocated to become Professor and Department Chair of the Molecular Biology and Biophysics at the University of Connecticut School of Medicine (12/2020). The environment at UCHC is exceptional, focused on advancing biomedical research and discoveries and I mentored the first junior hire to get an NIH DP2 award and I was able to hire two exceptional new tenure-track faculty to UCHC (one minority candidate) in one year.

I have also demonstrated significant research output (~142 papers) from NIH funded projects using a broad variety of cellular, biochemical and biophysical tools. Lastly, I have taken leadership position, e.g., for shared instrumentation, graduate education, departments and divisions. Clearly, my training, as well as my track record as an independent researcher, makes me uniquely qualified for this proposal. I have trained over thirty graduate and postdoctoral students from numerous programs; with all of them being able to successfully competing for jobs in academia and industry. Lastly, I am Associate Editor for the Journal of Biological Chemistry.

Here I am excited to continue my longstanding collaboration with Dr. Rebecca Page to understand the function of PPPs, especially how they recruit substrates and how they control essential biological functions. Results from this work will be critical to further our understanding of PPPs.

Ongoing Research Support

1R01AI141522-01A1 (MPI: **Peti, W.**; Rice, L.) 05/09/2019 – 4/30/2024

NIH/NIAID
Mechanism and activity of beta-lactam resistant enzymes in E. faecium and E. faecalis
The major aim is to understand how penicillin binding proteins become antibiotic resistant but main their functionality for substrates.

1R01HL151306-01A1 (PI: Bottini, N.; Collaborator: **Peti, W.**) 09/20/2019 – 6/30/2023
NIH/NIAMS
Role of PTP4A1 in systemic sclerosis

Completed Research Support

1R01NS091336-05 (MPI: **Peti, W.**; Page, R.) 02/01/2015 – 12/31/2020
NIH/NINDS
Serine/Threonine Phosphatases in Neurological Diseases
The aim of this proposal is to determine the structure of phosphatases, especially calcineurin (PP2B), to understand their function in Down Syndrome and Alzheimer's Disease.

1R01GM098482-09 (PI: Page, R.; Collaborator: **Peti, W.**) 09/01/2011 – 12/31/2020
NIH/NIGMS
PP1 regulation in the nucleus
The major aim is to determine the structure of regulatory PP1 holoenzyme structures to understand their function in RNA splicing and chromatin remodeling.

1R01GM134683-01 (PI: **Peti, W.**) 07/01/2019 – 12/31/2020
NIH/NIGMS
Protein Phosphatase 1 Holoenzyme Formation and Subunit Exchange
The major aim is to understand the biogenesis of PP1.

B. Positions, Scientific Appointments, and Honors
Positions and Scientific Appointments

12/2020-present	Department Chair, Molecular Biology & Biophysics, School of Medicine, University of Connecticut Health Center, Farmington, CT
12/2020-present	Professor (tenured), Molecular Biology & Biophysics, School of Medicine, University of Connecticut Health Center, Farmington, CT
1/2017-12/2020	Professor (tenured), Chemistry & Biochemistry, College of Medicine, University of Arizona, Tucson, AZ
7/2015-12/2016	Professor (tenured), Department of Molecular Pharmacology, Physiology and Biotechnology and Department of Chemistry, Brown University, Providence, RI
7/2012-12/2016	Director Biomolecular Interaction and Structural Biology Core Facility, Brown University, Providence, RI
7/2010-6/2015	Associate Professor (tenured), Department of Molecular Pharmacology, Physiology and Biotechnology and Department of Chemistry Brown University, Providence, RI
7/2007-6/2010	Manning Assistant Professor for Medical Science
7/2006-8/2010	Director Molecular Pharmacology & Physiology Graduate Program
9/2004-6/2010	Assistant Professor, Department of Molecular Pharmacology, Physiology and Biotechnology and Department of Chemistry, Brown University, Providence, RI
10/2001-8/2004	Postdoctoral Fellow, Laboratory of Dr. Kurt Wüthrich, Department of Molecular Biology, The Scripps Research Institute, La Jolla, Ca
4/1998-9/2001	Graduate Student, Laboratory of Dr. C. Griesinger, Department of Chemistry, Johann-Wolfgang Goethe University, Frankfurt, Germany
1/1998-3/1998	Research Assistant, Laboratory of Dr. J. Stetter, Central Laboratories, Bayer AG, Leverkusen, Germany
2/1997-12/1997	Diploma student Laboratory of Dr. B.K. Keppler, Department of Chemistry, University of Vienna, Vienna, Austria

Honors

2020	2020 Excellence in Postdoctoral Mentoring Award, University of Arizona

7/2018-6/2020	Chair – NIH MIST Study Section
2/2017-present	Associate Editor, The Journal of Biological Chemistry
1/2017-12/2020	Homer C. and Emily Davis Weed Chair; University of Arizona, Tucson, AZ
2014-2019	American Diabetes Association Pathway Fellow
7/2007-6/2010	Manning Assistant Professor
2005	Rhode Island Foundation Award
2005	Richard B. Salomon Faculty Research Award
2004	Max-Kade Foundation Fellowship Award
2002-2004	Erwin-Schrödinger-Stipend (FWF/Austria)
2002	Ernst Award 2002 of the German Chemical Society
2001	Ph.D. degree, *summa cum laude*, at the Johann-Wolfgang Goethe University, Frankfurt
1998-2000	Member of the University Sponsor group of the Bayer AG
1998-2001	Kekulé thesis scholarship from the scholarship fund of the association of the chemical industry in Germany
12/1997	Graduated *summa cum laude* in Chemistry at University of Vienna, Vienna
1996-1998	Performance scholarship of the ministry for science and culture in Austria

Other Experience and Professional Memberships

2004-present	ACS member
2006-present	ASPET member
2007-present	Protein Society member
2010-present	ASBMB member
2013-present	American Crystallographic Association member
2001-present	*Ad hoc referee for:* Nature Structural Molecular Biology, Nature Chemical Biology, Nature Methods, Structure, J Biol Chem, JACS, Biochemistry, J Mol Biol, Protein Science,…
2005	Temporary Member ZRG1 F04B 20 Study Section
2008-present	NSF Reviewer; Division of Chemistry and Division of Molecular and Cellular Biosciences
2011-present	NSF (Division of Molecular and Cellular Biosciences), Biomolecular Systems, Molecular Biochemistry, Panel Member
2011-present	Member of the NSLS Facility Proposal Review Panel – Structural Biology in Solution – Brookhaven National Laboratories
2012-2015	Temporary Member NIH MIST Study Section (2012/2014/2015)
2013-present	Member of the ALS Facility Proposal Review Panel – Structural Biology in Solution – Lawrence Berkeley National Laboratories
2014	Temporary Member NIH MSFB Study Section
2016-2020	Permanent Member NIH MIST Study Section
2018-2020	Chair – NIH MIST Study Section
2010-2015	Contributing Member of “Faculty of 1000”
2013-2016	Editorial Board Member of the *Journal of Biological Chemistry*
2017-present	Associate Editor (Structural Biology, Molecular Mechanism of Signal Transduction, Phosphates, NMR spectroscopy, X-ray crystallography and cryo-EM) of the *Journal of Biological Chemistry*

C. Contributions to Science (Selected from 142 peer-reviewed publications)

(i) **Regulation of serine/threonine Phosphatases:** Ser/Thr protein phosphatases (PSP) are a family of signaling enzymes that are woefully understudied, as for the longest time it was assumed that they are housekeeping enzymes and that all specificity is derived from the action of kinases. Our work has been central to provide a molecular picture that showed that this “housekeeping idea” is wrong; rather PSPs are similarly specific, or more specific, than kinases. PP1, the ubiquitous PSP, is controlled by more than 200 regulatory proteins, which form specific holoenzymes to control substrate specificity directly and indirectly (e.g. by localization). We have shown that one mechanism used by PP1 to become substrate specific is by sterically excluding sets of substrates. This mode of action has been now also observed for PP3 (Calcineurin) and PP2A. PP1, PP2A and PP3 have critical roles in cellular processes as diverse as protein synthesis and cell cycle progression. Thus, specific PP1 inhibitors and/or activators hold enormous clinical potential for the treatment of a large variety of diseases, but especially cancer. By using

a combination of cell biology, biochemistry and biophysics, we are elucidating, at a molecular level, how PP1/PP2A/PP3 are differentially regulated by distinct targeting proteins. Our work is not only providing a new paradigm for understanding the structural basis of PP1 regulation in all tissues, but is also laying the structural foundation for establishing PP1 as a highly specific drug target.

Ragusa, M.J., Dancheck, B., Critton, D.A., Nairn, A.C., Page, R. & **Peti, W.** (2009) Spinophilin directs Protein Phosphatase 1 specificity by steric inhibition of substrate binding sites, *Nature Structural & Molecular Biology*, 7(4):459-464. PMCID: PMC2924587

Li, Y., Sheftic, S.R., Grigoriu, S., Schwieters, C., Page, R. & **Peti, W.** (2020) The structure of the RCAN1:CN complex explains the inhibition of and substrate recruitment by calcineurin, *Science Advances*, 6:eaba3681. PMCID: PMC7458460

Grigoriu, S., Bond, R., Cossio, P., Chen, J.A., Ly, N., Hummer, Page, R., Cyert, M.S., **Peti, W.** (2013) The molecular mechanism of substrate engagement and immunosuppressant inhibition of Calcineurin. *PLoS Biology*, 11(2):e1001492. PMCID: PMC3582496

Kumar, G.S, Choy, M.S., Koveal, D.M., Lorinsky, M.K., Lyons, S.P., Kettenbach, A.N., Page, R. & **Peti, W.** (2018) Identification of the Substrate Recruitment Mechanism of the Muscle Glycogen Protein Phosphatase-1 Holoenzyme, *Science Advances*, 4:eaau6044. PMCID: PMC6235537

(ii) **Drug Design for Protein Tyrosine Phosphatases:** Tyr-phosphatases use multiple surface exposed loops to dephosphorylate substrates. This includes the PTP-, WPD-, the Q- and the substrate binding loop. But how is the catalytic cycle coordinated at a molecular level and are some loop movements dependent on the movements of others? We study a variety of tyr-phosphatases (PTPN5 [STEP], PTPN7 [HePTP] and PTPN1[PTP1B]) in order to identify the similarities and differences of the enzymatic cycle within this family of critical enzymes.

Our initial studies on PTP1B focused on novel approaches for developing highly potent and specific inhibitors, highlighted by our discovery that it is possible to design specific inhibitors against flexible intrinsically disordered regions, *an entirely new concept for drug design*. However, by doing so we gained insight into 'spine'-like (spines have been defined for kinases as critical for function by Prof. Taylor, UCSD) communication networks within PTP1B; however, the communication is based on dynamics rather than conformational changes. While PTP1B and TCPTP have a ~80% identical catalytic domain, we have recently shown that its intrinsically disordered C-terminal tail creates their specificity – highlight the importance of IDRs for enzyme function

Choy, M.S., Li, Y., Machado, L.E.S.F., Kunze, M.B.A., Connors, C.R., Wei, X., Lindorff-Larsen, K., Page, R. & **Peti W.** (2017) Conformational rigidity and protein dynamics at distinct timescales regulate PTP1B activity and allostery, *Molecular Cell*, 65, 644-658. PMCID: PMC5325675

Krishnan, N., Krishnan, K., Connors, C.R., Choy, M.S., Page, R., **Peti, W.**, van Aelst, L., Shea, S.D., & Tonks, N.T. (2015) Targeting BDNF signaling through inhibition of PTP1B suggests a novel therapeutic strategy for treatment of Rett syndrome, *Journal of Clinical Investigation*, 125(8), 3163-3177. PMCID: PMC4062594

Krishnan, N., Koveal, D., Miller, D.H., Kragelj, K., Ringkjøbing Jensen, M., Gauss, K., Xue, B., Muthuswamy, S.K., Page, R., Blackledge, M., **Peti, W.** & Tonks, N.K. (2014) A novel mechanism of allosteric inhibition of protein tyrosine phosphatase PTP1B reveals a new strategy for therapeutic development, *Nature Chemical Biology*, 10(7), 558-566. PMCID: PMC4062594

Singh, J.P, Li, Y., Chen, Y.-Y., Hsu, S.T.D., Page, R., **Peti W.** & Meng, T.C. (2022) The catalytic activity of TCPTP is auto-regulated by its intrinsically disordered tail and activated by Integrin alpha-1, *Nature Communication*, 13:94. PMCID: PMC8748766

(iii) **Regulation of the mitogen activated kinases**: Mitogen-activated protein kinases (MAPKs; ERK, p38, JNK) are a family of ser/thr kinases that mediate cellular responses to a variety of extracellular stimuli, including growth factors and cytokines. Disruptions in the tight regulation of MAPK signaling pathways are directly correlated with numerous diseases, including Alzheimer's disease, rheumatoid arthritis and cancer. MAPK activation is finely-tuned in a cell-type specific and temporal manner by MAPK regulatory proteins, including activating kinases (MEK1, MKK3, MKK6) and deactivating phosphatases (KIM-PTPs [e.g. HePTP, STEP, PTPRR], DUSPs).

Recently, we developed an integrated approach, including NMR spectroscopy, ITC and SAXS, to obtain an accurate model of the p38:HePTP complex, the first of any MAPK bound to a regulatory protein. We expanded this work to gain additional structural insights into the complete family of MAPK regulatory

complexes and showed provided a mechanistic model for the different regulation of the MAPK PTP family members. We were interested in how scaffolding influences signaling and investigated how the ERK2 scaffolding protein KSR1 becomes targeted to the membrane in order to be in close proximity to B-Raf. We showed that the CA1 domain has a new fold and that this fold can interact in a unique manner with the membrane. Lastly, we showed how dynamics at different timescales allow for the activation of p38.

Francis, D., Koveal, D., Rozycki, B., Hummer, G., Page, R. & **Peti, W.** (2011) Structural basis of p38α regulation by hematopoietic tyrosine phosphatase*, Nat Chem Biol*., 7(12), 916-924. PMCID: PMC3657131
Koveal, D., Schuh, N., Ritt, D., Page, R. Morrison, D.K., & **Peti, W.** (2012) Discovery of a new domain in KSR scaffolds that mediates plasma membrane targeting, *Science Signaling,* 5 (525), ra94. PMCID: PMC3740349
Francis, D.M., Kumar, G.S., Koveal, D., Tortajada, A., Page, R. & **Peti, W.** (2013) The differential regulation of p38α by the neuronal KIM-PTPs, a detailed molecular study, *Structure*, 21(9), 1612-1623. PMCID: PMC3769431
Kumar, G.S, Clarkson, M., Kunze, M.B.A., Granata, D., Wand, A.J., Lindorff-Larsen, K., Page, R., & **Peti, W.** (2018) Dynamic Activation and Regulation of the Mitogen-activated protein kinase p38, *PNAS*, 115(18), 4655-4660. PMCID: PMC5939092

(iv) **Bacterial Toxin-Antitoxin systems:** My laboratory has made significant contributions in the molecular analysis of different TA systems, including the detection of a novel Type V TA system.

Brown, B.L., Grigoriu, S., Kim, Y., Arruda, J., Davenport, A., Wood, T.K., **Peti, W.** & Page R. (2009) Three Dimensional Structure of the MqsR:MqsA Complex: a Novel TA Pair comprised of a Toxin Homologous to RelE and an Antitoxin with Unique Properties, *PLoS Pathog* 5(12): e1000706. PMCID: PMC2791442
Brown, B.L., Wood, T.K., **Peti, W.** & Page R. (2011) Structure of the *E. coli* Antitoxin MqsA bound to its Gene Promotor reveals extensive Rearrangements and the Specificity of Transcriptional Regulation, *J Biol Chem,* 286 (3), 2285-2296. PMCID: PMC3023523
Wang, W., Kim, Y., Ma, Q., Hong, S.H., Brown, B.L., Benedik, M.J., **Peti, W**., Page, R. & Wood, T.K. (2011) Antitoxin MqsA Helps Mediate the Bacterial General Stress Response, *Nat Chem Biol*, 7(6), 359-366. PMCID: PMC3097263
Wang, X., Lord, D.M., Cheng, H.-Y., Osbourn, D.O., Hong, S.H., Sanchez-Torres, V., Quiroga, C., Herrmann, T., **Peti, W.**, Benedik, M.J., Page, R. & Wood, T.K. (2012) Persister Cell Formation Depends on a Cascade of Toxin/Antitoxin Systems Involving Antitoxin Cleavage of Toxin RNA, *Nat Chem Biol*, 8, 855-861. PMCID: PMC3514572

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1r3ohqhUnObkn/bibliograpahy/48155234/public/?sort=date&direction=ascending

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES**

NAME: Sathish Padi

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

POSITION TITLE: Assistant Professor (In Residence), Basic Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University College of Pharmaceutical Sciences, KU, INDIA	Bachelors in Pharmacy	02/2004	Pharmaceutical Sciences
University of Detroit Mercy, Detroit, MI	MS	08/2008	Chemistry
North Dakota State University, Fargo, ND	PhD	09/2013	Cancer Biology
Medical University of South Carolina, Hollings Cancer Center, Charleston, SC	Postdoc	09/2014	Cancer Biology
University of Arizona Cancer Center, Tucson, AZ	Postdoc	04/2019	Cancer Biology

A. Personal Statement

Understanding comprehensive signaling pathways and mechanisms contributing to drug resistance in cancer cells is my long-term career aspiration. To pursue these, I plan to leverage my extensive training in diverse fields of cancer pharmacology, epigenetics, cell and molecular biology. As a graduate student in Dr. Bin Guo's laboratory, I identified miR-627 and JMJD1A- as potential targets to exploit the antitumor activity of vitamin D without eliciting its hypercalcemic side effect. This research was published in the high impact journal Gastroenterology. Due to my outstanding contributions to graduate research, I received numerous awards during my PhD, the Young Investigator Award from SEBM, best graduate student award among others.

As a post-doc in Dr. Andrew S Kraft's laboratory, I addressed the role of PIM kinases on the growth of hematological and solid tumors and elucidating its role in conferring resistance to drug treatment in prostate and breast cancers by utilizing PDXs, mouse models, cancer cell lines, organoids and novel PIM inhibitors. We identified, for the first time, that the PIM kinases phosphorylate novel substrates like IRS1, DEPDC5, and EDC3 in various cancer cell lines. I spearheaded projects that unraveled many novel mechanisms underlying drug resistance in various cancers. I was awarded the ASH travel award to present my research. In a different project, I studied the mechanism of DEPDC5 phosphorylation by PIM kinases, a novel mTORC1 regulatory mechanism that establishes PIM as an upstream effector of mTORC1 to promote tumor growth. This study is significant in the context that it reveals a previously unreported mechanistic link between mTORC1 and PIM kinase. For this research, I received the Scholar in training award, one of the most reputed awards for young career scientist presented by the AACR. The research was published in PNAS. In my third project, a collaboration study with Wolfgang Peti's laboratory, we demonstrated that PIM kinases binds to the P-body protein, Enhancer-of-mRNA-decapping-3 (EDC3), and phosphorylates EDC3 on serine (S)161 and this phosphorylation regulates multiple cancer-relevant functions. This research is published in EMBO Reports.

To gain knowledge and further understand the molecular insights into the substrate specificity of Serine/Threonine Kinases and Protein Phosphatases, I joined the laboratory of Drs. Wolfgang Peti and Rebecca Page as an Assistant Professor (In Residence)/Basic Sciences at UConn Health, Molecular Biology and Biophysics Department. Their labs provide an exciting environment for my scientific growth. Frequent interactions with scientists and clinicians through meetings and seminars, aids in awareness about novel approaches in

understanding and treating various cancers. My current goal is to achieve an in-depth understanding of signaling networks with a special focus on serine/threonine kinase and phosphatase signaling-using chemical, biochemical, biophysical and structural biology (NMR spectroscopy, X-ray crystallography and especially cryo-EM) techniques.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-Current	Assistant Professor (In Residence), University of Connecticut School of Medicine, Farmington, CT
2019 - 2020	Scientist III. University of Arizona, Tucson, AZ
2013 - 2019	Postdoctoral Research Associate, Laboratory of Dr. Andrew S Kraft, Hollings Cancer Center, Charleston, SC and University of Arizona Cancer Center, Tucson, AZ
2010 - 2012	Teaching Assistant, Pharmaceutical Sciences, North Dakota State University, Fargo, ND
2008 - 2013	Graduate Assistant, Pharmaceutical Sciences, North Dakota State University Fargo, ND
2006 - 2007	Teaching Assistant, Chemistry and Biochemistry, University of Detroit Mercy, Detroit, MI.
2005 - 2008	Graduate Assistant, Chemistry and Biochemistry, University of Detroit Mercy, Detroit, MI
2004 - 2005	Senior Scientific Content Developer. (Medical Writer), Foot Prints, Hyderabad, India
2003	Trainee: Industrial in-plant training at Cadila Pharmaceuticals, Ahmedabad, India

Honors

2020	PIM kinase inhibitors block the growth of primary T-cell acute lymphoblastic leukemia: Resistance pathways identified by network modeling analysis – Featured in Highlights of Molecular Cancer Therapeutics journal -September 2020 | Volume 19 | Issue 9
2018	Invited/selected for a short talk in a plenary session at the AACR Special Conference on Targeting PI3K/mTOR Signaling, Boston, MA.
2018	Scholar-in-Training Award supported by Aflac, Inc. AACR Special Conference on “Targeting PI3K/mTOR Signaling”, Boston, MA.
2016	ASH Abstract achievement award, 58th ASH Annual Meeting & Exposition, San Diego, CA.
2014	Post-doctoral scholarship from Abney and Associates foundation, Anderson, SC
2013	Graduate Student Travel Award from ASPET (American Society for Pharmacology & Experimental Therapeutics)
2013	Young Investigator Award from SEBM (Society for Experimental Biology and Medicine):
2012-2013	Darryle and Clare Schoepp Graduate Research Scholarship, by the NDSU College Scholarship Recognition Committee
2012-2013	Treasurer of AAPS-NDSU Student Chapter
2011-2013	ND EPSCoR-DDA Award at NDSU (North Dakota Experimental Program to Stimulate Competitive Research - Doctoral Dissertation Assistantship)
2010	Certificate from “The Honor Society of Phi Kappa Phi”, North Dakota State University

Other Experience and Professional Memberships

2011-Present	American Association for Cancer Research (AACR)
2016-2019	American Society of Hematology (ASH)
2016-Present	Editorial member of Austin Journal of Medical Oncology and Cancer Clinical Research Reports
2016-Present	Manuscript Reviewer for Molecular Cancer Therapeutics, Oncotarget, Blood and Lymphatic Cancer, Leukemia Research, OncoTargets and Therapy, and International Journal of Hematology, Blood Reviews, Cancers, Life

C. Contribution to Science

(i) **Synthesis and Characterization of Novel Bis-bidentate ligands:** As a master student under the guidance of Dr. Benvenuto my research was focused on the synthesis and characterization of a new bis-bidentate ligand incorporating 2, 6-diaminotoluene. The ligand is produced using the well-established Schiff's base condensation, and can be crystallized from polar solvent. Characterization was done via NMR spectroscopy and single crystal diffraction. The ligand, its structure, and its reactivity towards metal ions were discussed in the thesis.

Sathish Padi, Jason Cebulski, Brandon Korfel, Mark A. Benvenuto. Synthesis of a series of novel bis-bidentate ligands utilizing 2,6-diaminotoluene. 233rd American Chemical Society (ACS) National Meeting, Chicago, IL, March 25-29, 2007 (Poster Presentation).

Sathish Padi, Brandon Korfel, Mark A Benvenuto. Synthesis and characterization of a new bis-bidentate ligand incorporating 2,6-diaminotoluene. 236th American Chemical Society (ACS) National Meeting, Philadelphia, PA, August 17-21, 2008 (Oral Presentation).

(ii) **Epigenetic Mechanisms and Drug Resistance:** As a PhD student under the guidance of Dr. Bin Guo, my research was focused on the understanding of how epigenetic mechanisms contribute to drug resistance mainly in colon cancer and prostate cancer. We identified the novel targets (miR-627 & JMJD1A) downstream of vitamin D, which can be used to design a new therapy for colon cancer and these results were published in "Gastroenterology" (**impact factor 22.68**), the most cited journal in the field of gastrointestinal diseases. This work resulted in an NIH R01 grant to Dr. Bin Guo "RNA Therapeutics for Targeted Treatment of Colon Cancer" (R01 CA186100-01A1; 5/19/2015–4/30/2019; $1,351,550).

Bhatnagar N*, Li X*, **Padi SK***, Zhang Q, Tang MS, Guo B. (**2010**) Downregulation of miR-205 and miR-31 confers resistance to chemotherapy-induced apoptosis in prostate cancer cells. **Cell Death and Disease**, 1, e105; doi:10.1038/cddis.2010.85. PMCID: PMC3004480 (* Co-first author*, cited by 214 articles*)

Padi SK, Guo B. MiR-627 mediates the epigenetic mechanism of vitamin D in suppression of colon cancer growth both in vitro and in vivo. **EB conference**, **2013**. The **FASEB** Journal 27 (1_supplement), 1104.5.

Padi SK, Guo B. MiR-627 and histone demethylase JMJD1A as new therapeutic targets in colon cancer. **AACR**, **2012**. **Cancer Research** 2012;72(8 Suppl): Abstract nr 4739.

Padi SK, Zhang Q, Rustum YM, Morrison C, Guo B. (**2013**) MicroRNA-627 Mediates the Epigenetic Mechanisms of Vitamin D to Suppress Proliferation of Human Colorectal Cancer Cells and Growth of Xenograft Tumors in Mice. **Gastroenterology**. doi: 10.1053/j.gastro.2013.04.012. PMCID: PMC3722307 (Frist author, *cited by 111 articles*)

(iii) **Collaboration work with other researchers at North Dakota State University.**

Zhang Q, **Padi SK**, Tindall DJ, Guo B. (**2014**) Polycomb protein EZH2 suppresses apoptosis by silencing the proapoptotic miR-31. **Cell Death and Disease**. doi:10.1038/cddis.2014.454. PMCID: PMC4237267 (*cited by 77 articles*)

Kulkarni PS, Haldar MK, Nahire RR, Katti P, Ambre AH, Muhonen WW, Shabb JB, **Padi SK**, Singh RK, Borowicz PP, Shrivastava DK, Katti KS, Reindl K, Guo B, Mallik S. (**2014**). MMP-9 Responsive PEG Cleavable Nanovesicles for Efficient Delivery of Chemotherapeutics to Pancreatic Cancer. **Molecular Pharmaceutics**. doi: 10.1021/mp500108p. PMCID: PMC4096225 (*cited by 82 articles*)

Singh RK, Cho K, **Padi SK**, Yu J, Haldar M, Mandal T, Yan C, Cook G, Guo B, Mallik S, Srivastava DK. (**2015**) Mechanism of N-Acylthiourea-mediated Activation of Human Histone Deacetylase 8 (HDAC8) at Molecular and Cellular Levels. **The Journal of Biological Chemistry**. doi: 10.1074/jbc.M114.600627. PMCID: PMC4358293 (*cited by 20 articles*)

(iv) **PIM kinases: A potential therapeutic target in T-cell Acute Lymphoblastic Leukemia:** For my Post-doctoral training, I joined the laboratory of Dr. Andrew S Kraft, Professor and Director of the University of Arizona Cancer Center, where I got an opportunity to investigate the role of PIM oncogenic kinases in hematopoietic and solid tumor malignancies. Dr. Kraft's lab has been a leader in the study of PIM kinases, and successfully synthesized and developed a PIM kinase inhibitor (SMI-4a), which validated PIM as a relevant therapeutic target in cancer. Under the mentorship of Dr. Kraft, I have made a novel observation that PIM1 is overexpressed in early T cell precursor (ETP)-ALL, a subset of T-ALL, which are shown to be chemo-refractory due to their heterogeneous nature along with activating mutations. This, together with our observation that combining PIM inhibitors with Ponatinib, an oral multi-targeted tyrosine kinase inhibitor induces substantial apoptosis of ETP-ALL cells, will enhance the development of a new therapeutic option towards significantly blocking the T-ALL growth in pre-clinical setting, and in the future for children and adults with difficult to treat T-ALL.

Padi SK, Luevano LA, An N, Pandey R, Singh N, Song JH, Aster JC, Yu XZ, Mehrotra S, and Kraft AS. (**2017**) Targeting the PIM Protein Kinases for the Treatment of a T-cell Acute Lymphoblastic Leukemia Subset. **Oncotarget**. doi: 10.18632/oncotarget.16320. PMCID: PMC5444737 (*cited by 33 articles*)

Song JH, **Padi SK**, Luevano LA, Minden MD, DeAngelo DJ, Hardiman GT, Ball LE, Warfel NA, and Kraft AS. (**2016**) Insulin Receptor Substrate 1 Is a Substrate of the Pim Protein Kinases. **Oncotarget**. doi: 10.18632/oncotarget.7918. PMCID: PMC49914444 (*cited by 24 articles*)

Singh N, **Padi SK**, Bearss JJ, Pandey R, Okumura K, Beltran H, Song JH, Kraft AS, and Olive V. **(2020)** PIM protein kinases regulate the level of the long noncoding RNA H19 to control stem cell gene transcription and modulate tumor growth. **Molecular Oncology.** PMID: 32146726 *(cited by 13 articles)*

Lim JT, Singh N, Leuvano LA, Calvert VS, Petricoin EV, Teachey D, Lock R, Padi M, Kraft AS*, and **Padi SK*. (2020)** PIM kinase inhibitors block the growth of primary T-cell acute lymphoblastic leukemia: Resistance pathways identified by network modeling analysis. ***Corresponding author**; **Molecular Cancer Therapeutics**. PMID: 3275338 *(cited by 1 article)*

(v) **Targeting PIM kinases to overcome drug resistance mechanisms:** Researchers have provided a rationale and basis for co-targeting PIM kinases with inhibitors of PI3K/mTOR/AKT, JAK/STAT, MYC, stemness, and RNA Polymerase I transcription, along with other treatments, including androgen deprivation therapy, radiotherapy, chemotherapy, and immunotherapy. Such combined approaches could potentially be used as neoadjuvant therapies, limiting the development of resistance to treatments or sensitizing cells to other therapeutics. We have identified a phosphorylation-dependent mechanism that controls mTORC1 activity in which Pim and AKT kinases, 2 enzymes with increased activity in cancer phosphorylate DEPDC5, a member of the GATOR1 complex that senses cellular amino acid levels. The critical nature of this substrate to the activity of these protein kinases is demonstrated by the fact that deletion or mutation of DEPDC5 partially blocks the ability of Pim and Pim plus AKT inhibitors to suppress tumor cell growth. Thus, protein kinases regulate the amino acid sensing cascade to control mTORC1 activity and tumor cell growth.

Padi SK, Singh N, Mouneimne G, Kraft AS, Okumura K. Phosphorylation of DEPDC5 by the Pim-1 protein kinase, a cancer driver, stimulates mTORC1 activity by regulating the DEPDC5- Rag GTPase interaction. **AACR** Special Conference: Targeting PI3K/mTOR Signaling, **2018**, Boston, MA. (Oral and Poster presentation).

Padi SK, Singh N, Bearss JJ, Olive V, Song JH, Cardó-Vila M, Kraft AS, and Okumura K. (**2019**) Phosphorylation of DEPDC5, a component of the GATOR1complex, releases inhibition of mTORC1 and promotes tumor growth. **Proceedings of the National Academy of Sciences.** PMID: 31548394 *(cited by 9 articles)*

Song JH, Singh N, Luevano LA, **Padi SK**, Okumura K, Olive V, Black SM, Warfel NA, Goodrich DW, and Kraft AS. (**2018**) Mechanisms behind resistance to PI3K Inhibitor treatment induced by the PIM kinase. **Molecular Cancer Therapeutics.** PMID: 30190422 *(cited by 25 articles)*

Bearss JJ#, **Padi SK#**, Singh N, Cardó Vila M, Song JH, Mouneimne G, Fernandes N , Li Y, Harter MR, Gard JMC, Cress A, Peti W, Nelson A, Buchan JR, Kraft AS and Okumura K. (**2021**) EDC3 phosphorylation regulates growth and invasion through controlling P-body formation and dynamics. **EMBO Reports**. PMID: 33586867 (# Co-first author, *cited by 4 articles*)

Complete List of Published Work in MyNCBI:

https://www.ncbi.nlm.nih.gov/myncbi/1DA2BafVhvXIk0/bibliography/public/