BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Ma, Qianqian

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

POSITION TITLE: Postdoc Fellow

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)	START DATE MM/YYYY	COMPLETION DATE MM/YYYY	FIELD OF STUDY
China Agricultural University, Beijing, Beijing	BS	09/2006	07/2010	Biological Sciences
Miami University, Oxford, OH	PHD	08/2010	12/2016	Cell, Molecular & Structural Biology
Johns Hopkins University, Baltimore, MD	Postdoctoral Fellow	02/2019	present	Structural Biology, Lipid Biochemistry

A. Personal Statement

My research focuses on protein structure and protein-lipid interaction and how they correlate with each other in biological systems. As a graduate student, I worked on characterization of a protein transport pathway in chloroplasts by using different biochemistry tools as well as using transmission electron microscope to look at the morphology change of mutant chloroplasts in the cellular level. To extend my experience in structural biology, I decided to learn cryoEM, one of the most powerful tools to exam the biological samples with atomic resolution. To make a smooth transition from studying plant biology at cellular level to protein structure at single particle level, I then worked as a research specialist in Dr. Dan Raben lab and focused on protein expression and purification of a human lipid kinase DGKq and prepared sample for cryoEM studies.DGKq is a lipid kinase modulating lipid signal molecules. Increasing evidence has pinpointed its critical roles in neuronal disease. Structural insights of DGKq will greatly benefit the understanding of its catalytic mechanism and further guide drug design. During my postdoc training, I carried on the structural study of DGKq. In collaboration with Dr. Sandra Gabelli, we have optimized DGKq expression from insoluble bacterial system or low yield HEK293 cells to high yield/high purity from Sf9 insect cells. CryoEM studies with high quality DGKq protein reveals the first mammalian DGK structure since they were identified over six decades ago. We are now gaining substantial insight into the architecture and regulation of this dynamic lipid kinase.

1. Ma Q, Srinivasan L, Gabelli SB, Raben DM. Elusive structure of mammalian DGKs. Adv Biol Regul. 2022 Jan;83:100847. PubMed Central PMCID: PMC8858910.
2. Ma Q, Gabelli SB, Raben DM. Diacylglycerol kinases: Relationship to other lipid kinases. Adv Biol Regul. 2019 Jan;71:104-110. PubMed Central PMCID: PMC6347529.

B. Positions and Honors

Positions and Scientific Appointments

2019 - Postdoc Fellow, Department of Biological Chemistry, Johns Hopkins University, Baltimore, MD
2016 - 2019 Research specialist, Department of Biological Chemistry, Johns Hopkins University, Baltimore, MD

Honors

2020	Helmsley Fellowship for CSHL cryoEM course, Helmsley Charitable Trust
2013	ASPB Travel Award, ASPB
2009	Scholarship, Continent Biotech, Beijing, China
2008	Scholarship, Kerry Oils & Grains, Beijing, China
2007	Scholarship for Excellent Student, China Agricultural University

C. Contribution to Science

1. Graduate Career: My graduate research focused on protein transport in chloroplasts. I characterized Hcf106, one of the major components in Tat (Twin Arginine Translocation) pathway. We successfully integrated in vitro expressed Hcf106 into the isolated chloroplasts. Further BN-PAGE analysis allowed us to identify the locations of amino acids in Hcf106 that were critical for interacting with another component, cpTatC. Comprehensive cross-linking experiment further allowed us to map interactions of the transmembrane domain and amphipathic helix region of Hcf106. A novel model for Tat transport was built based on our findings. I also genetically and developmentally characterized how defected Tat pathway affects chloroplast biogenesis and how it affects the plastid-to-nucleus retrograde signaling pathway.

    a. New CP, Ma Q, Dabney-Smith C. Routing of thylakoid lumen proteins by the chloroplast twin arginine transport pathway. Photosynth Res. 2018 Dec;138(3):289-301. PubMed PMID: 30101370.
    b. Ma Q, Fite K, New CP, Dabney-Smith C. Thylakoid-integrated recombinant Hcf106 participates in the chloroplast twin arginine transport system. Plant Direct. 2018 Oct;2(10):e00090. PubMed Central PMCID: PMC6508782.

2. Postdoctoral Career: As a postdoctoral fellow, my research is focused on the structure and function of a lipid kinase, DGKq. DGKq is highly relevant to human disease as knockout of DGKq greatly affect synaptic vesicle recycling in neuron. I have developed and optimized the expression and purification of DGKq from both human suspension cells and insect cells. The purified DGKq demonstrated high kinase activity from in vitro kinase assay. We also performed HDX-MS experiment in collaboration with Dr. John Burke, characterized protein dynamics and illustrated a conformational change when DGKq substrate is present. Initial cryoEM data collection and processing demonstrated the overall architecture of DGKq. Further screening to identify sample with high resolution structure information is undertaking.

    a. Ma Q, Srinivasan L, Gabelli SB, Raben DM. Elusive structure of mammalian DGKs. Adv Biol Regul. 2022 Jan;83:100847. PubMed Central PMCID: PMC8858910.
    b. Ma Q, Gabelli SB, Raben DM. Diacylglycerol kinases: Relationship to other lipid kinases. Adv Biol Regul. 2019 Jan;71:104-110. PubMed Central PMCID: PMC6347529.

D. Scholastic Performance

Scholastic Performance

YEAR	COURSE TITLE	GRADE
	CHINA AGRICULTURAL UNIVERSITY	
	MIAMI UNIVERSITY	

X: Pass for credit/noncredit class

BIOGRAPHICAL SKETCH

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NAME: Raben, Daniel M

eRA COMMONS USER NAME (credential, e.g., agency login): DRABEN1

POSITION TITLE: Professor of Biological Chemistry, Physiology, and Oncology

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 Michigan-Ann Arbor	BS	1976	Biology/Chemistry
Washington University, St. Louis MO	PhD	1981	Biochemistry
University of California-Irvine	Postdoc.	1986	Biochemistry

A. Personal Statement

My graduate research was focused on contact inhibition wherein anchorage dependent cells stop growing when they reach a specific density. I characterized a membrane component involved in this process and partially purified the factor from isolated plasma membranes. At the time, it was known that the contact between adjacent cell membranes induced the inhibition of amino acid uptake. It was believed that this inhibition was an essential component of the contact-mediated cessation of cell growth. My work showed, however, that the contact-mediated inhibition of amino acid uptake was dissociated from the inhibition of cell growth. I followed these studies with postdoctoral work to examine the molecular mechanisms of agonist-induced lipid metabolism. It was during these studies that I demonstrated that two pathways are often stimulated: one pathway involved the hydrolysis of phosphatidylinositols (PtdIns(4,5)P_2 in particular), and a pathway independent of this PIP_2 metabolism. When I began his research program at Hopkins in 1986, it had been assumed that hydrolysis of phosphoinositides was solely responsible for the increased production of diacylglycerols following exposure of cells to mitogens. When I began these studies, there had been a controversy in the literature regarding the exclusive nature of the phosphoinositides as the sole source of agonist-induced diacylglycerols. One of the first major accomplishments in my laboratory was the development of a strategy which quantitatively analyzed the molecular species of cellular phospholipids and diacylglycerols. These analyses allowed studies in my laboratory to unequivocally demonstrate that the increased level of diacylglycerols in response to mitogens was not solely from PI, but largely from phosphatidylcholine. These results, and the approach we developed, had a major impact on the field regarding our understanding of the biochemistry and helped launch lipidomics as an important analytic approach. Further work from our laboratory discovered that much of the induced lipid metabolism occurred in the nuclear envelope or within the nucleus and involved the metabolism of nuclear phosphatidylcholine via a phosphatidylcholine-specific phospholipase D (PLD1b) and a diacylglycerol kinase-theta (DGK-θ). We then turned much of our attention to DGK-θ and found it to be present in the mammalian central nervous system. We have shown that the activity of this enzyme is regulated by an endogenous basic protein and plays a major role in synaptic vesicle recycling. Interestingly, PLD1, which catalyzes the production of the same product generated by DGK-θ activity has also been implicated in neurotransmitter release. Our current studies now focus on the structure, regulation and physiological roles of both DGK-θ and PLD1 in the central nervous system.

B. Positions and Honors

Positions and Employment

2007	Professor, Department of Biological Chemistry and Departments of Physiology and Oncology The Johns Hopkins University, Baltimore, Maryland
2002-2006	Associate Professor, Department of Biological Chemistry and Departments of Physiology and Oncology, The Johns Hopkins University, Baltimore, Maryland
1996-2006	Associate Professor; Department of Oncology The Johns Hopkins University, Baltimore, Maryland.
1991-2006	Associate Professor; Department of Physiology The Johns Hopkins University, Baltimore, Maryland.
1986-1991	Assistant Professor; Department of Physiology The Johns Hopkins University, Baltimore, Maryland.

Professional Service (selected)

2021	Chair "Molecular & Cellular Biology of Lipids" Gordon Research Conference
2019	Co-Chair "Molecular & Cellular Biology of Lipids" Gordon Research Conference FASEB Subcommittee on Training and Career Opportunities
2013-2018	Session Chair "Molecular & Cellular Biology of Lipids" Gordon Research Conference NIH Ad Hoc Reviewer BMCT, BBM, OTC (SBIR) FASEB Subcommittee on Training and Career Opportunities Editor-in-Chief, *Journal of Bioenergetics and Biomembranes* Editorial Board, *Current Cancer Drug Targets*
2012-2021	Chair, ASBMB Meetings Committee
2012	Co-Chair ZRG NIH OTC 10
2012-2015	Chair, ASBMB Task Force on Graduate and Medical Education
2011-2016	KERN Lipid Conference Board of Directors
2011-2020	Editorial Board, Advances in Enzyme Regulation
2010-2020	Editorial Advisory Board, Progress in Lipid Research
2010-2015	Editorial Board, *The Journal of Biological Chemistry*
2009-2012	ASBMB Meetings Committee
2009	Founder and Director of the ASBMB Lipid Research Division Corresponding Member, Class of Physical Sciences, Academy of Sciences of Bologna

C. Contribution to Science

I am a recognized world leader in the biochemistry and physiological roles of lipid metabolism with an interest in glycerolipids. My focus has been on the mechanisms underlying the generation and regulation of these lipids as well as mechanisms underlying their physiological roles. This work has led to peer-reviewed publications in *Nature*, *Science STKE*, *CELL Reports*, *among others.*

1. Molecular Species Analyses of Diglycerides

As I began my career, I focused on understanding the sources and roles of diacylglycerol molecular species. I studied this in cultured fibroblasts responding to mitogenic stimulation. These studies identified phosphatidylcholine as a major source of induced diacylglycerols and was a major impetus for the development of other lipidomic approaches.

1. Pessin, M.S., **Raben, D.M**. (1989) Molecular species analysis of 1,2-diglycerides stimulated by α-thrombin in cultured fibroblasts. *J. Biol. Chem.* **264**(15):8729-8738.

2. Leach, K.L., Ruff, V.A., Wright, T.M., Pessin, M.S., **Raben, D.M.** (1991) Dissociation of protein kinase C activation and sn-1,2-diacylglycerol formation. Comparison of phosphatidylinositol- and phosphatidylcholine-derived diglycerides in α-thrombin-stimulated fibroblasts. *J. Biol. Chem.* **266**(5):3215-3221.
3. Pessin, M.S., Altin, J.G., Jarpe, M., Tansley, F., Bradshaw, R.A., and **Raben, D.M.** (1991) Carbachol stimulates a different phospholipid metabolism than nerve growth factor and basic fibroblast growth factor in PC12 cells. *Cell Regulation* **2**:383-390.
4. Wright, T.M., Willenberger, S., and **Raben, D.M.** (1992) Activation of phospholipase D by α-thrombin contributes to the formation of phosphatidic acid but not to observed increases in 1,2-diglycerides. *Biochem. J.* **285**:395-400.

2. Nuclear Lipid Metabolism

Following my initial studies, my lab discovered unrecognized lipid metabolism in the nucleus. These studies open up new interest in the presence and role of lipids in this organelle which continues to this day.

1. Leach, K.L., Ruff, V.A., Jarpe, M.B., Fabbro, D., Adams, L.D., and **Raben, D.M.** (1992) α-Thrombin stimulates nuclear diglyceride levels and differential nuclear localization of protein kinase C isozymes in IIC9 cells. *J. Biol. Chem.* **267**:21816-21822.
2. Jarpe, M.B., Leach, K.L., and **Raben**, **D.M.** (1994) α-Thrombin-induced nuclear *sn*-1,2-diacylglycerols are derived from phosphatidylcholine hydrolysis in cultured fibroblasts. *Biochemistry* **33**:526-534
3. Baldassare, J.J., Jarpe, M.B., Alferes, L., and **Raben, D.M.** (1997) Nuclear translocation of RhoA mediates the mitogen-induced activation of PLD involved in nuclear envelope signal transduction. *J. Biol. Chem.* **272**:4911-4914.
4. Bregoli, L., Baldassare, J.J., **Raben, D.M.** (2001), Nuclear DGK-θ Is Activated in Response to α-Thrombin. *J. Biol. Chem.* **276**: 23288-23295.

3. Enzymology and Roles of Diacylglycerol Kinase-θ

During studies to examine nuclear lipid metabolism we began to realize that a portion of the nuclear diacylglycerols were derived from PtdIns(4,5)P_2 but these were rapidly phosphorylated to phosphatidic acid. This prompted us to try to understand the regulation of the nuclear diacylglycerol kinase catalyzing this reaction, DGK-θ.

1. Tu-Sekine B, and **Raben, D.M.** (2012) Dual Regulation of DGK-θ: Polybasic Proteins Promote Activation by Phospholipids and Increase Substrate Affinity. *J. Biol. Chem.* **287**(50):41619-41627.
2. Barber C.N., **Raben, D.M.** (2017) Phosphatidic Acid and Neurotransmission. Adv. Biol. Regul. Jan;63:15-21.
3. Tu-Sekine, B., **Raben, D.M.** (2017) Measuring Diacylglycerol Kinase-θ Activity and Binding *Methods Enzymol.* 583:231-253.
4. Ma, Q., Gabelli, S.B., and **Raben, D.M.** (2019). Diacylglycerol Kinases: Relationship to Other Lipid Kinases *Adv.Biol. Regul.* Jan 71: 104-110.

4. DGK-θ and its Role in Synaptic Vesicle Cycling

Much of our most recent efforts have been devoted to understanding the role of DGK-θ in the central nervous system. This was inspired by observations that the homolog in *C. elegans* appeared to play a role in regulating acetylcholine release at neuromuscular junctions. We found that DGK-θ in mammalian neurons also played a role, albeit opposite role to that found in *C. elegans,* in modulating glutatmate release. We have discovered that DGK-θ plays an important role in modulating evoked endocytosis during synaptic vesicle cycling.

1. Goldschmidt, H.L., Tu-Sekine, B, Volk, L, Anggono, V, Huganir, R.L., and **Raben, D.M.** (2016) DGK-θ Activity is Required for Efficient Recycling of Presynaptic Vesicles at Excitatory Synapses. *Cell Reports.* **14**(2): 200-207..
2. Barber C., **Raben, D.M.** (2020) Role of DGKs in neurons: postsynaptic function? *Adv. Biol. Reg.* Jan:;**75**100688.
3. Ma, Q., Srinivasan, L., Gabelli, S.B., **Raben, D.M.** (2021) Elusive Structure of Mammalian DGKs. *Adv. Biol. Reg.* Dec2; 100847.

4. Barber C.N., Goldschmidt, H.L., Ma, Q., Devine, L.R., Cole, R.N., Huganir, R.L. Raben, D.M. (2022) Identification of Synaptic DGK-θ Interactors That Stimulate DGK-θ Activity. Frontiers in Neuroscience. *In press*.

For a Partial List of published works (60/78) see MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/42561260/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

Multi-PI Proposal submitted.

Completed Research Support (selected since 2001)

RO1 NS077923 Raben (PI) 05/01/13-4/30/18
Biochemistry and Physiological Role of Diacylglycerol Kinase Theta
In this proposal we showed that DGK-θ requires a polybasic protein for full activity and provided the data showing this enzyme is involved in modulating evoked endocytosis during synaptic vesicle cycling.
Role: PI

R01 GM059251 Raben (PI) 9/1/05- 9/31/09
Coordinate Regulation of Nuclear DGK-θ and PLD
The major goal of this proposal was to examine the role of PLD and DGK-θ in metabolizing nuclear lipids in response to mitogens.
Role: PI

R01 HL079396 Raben (PI) 7/1/01 – 6/30/04
Regulation of α-Thrombin-induced Nuclear DGK-θ
In this proposal we demonstrated the localization and activation of DGK-θ in the nucleus of cells stimulated by α-thrombin which formed the basis of many of our nuclear studies.
Role: PI

BIOGRAPHICAL SKETCH

NAME: Sandra B. Gabelli

eRA COMMONS USER NAME: sgabell1

POSITION TITLE: Associate Professor

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	Completion Date	FIELD OF STUDY
Universidad Nacional del Sur	Licenciatura	1988	Computer Science
Johns Hopkins University – School of Medicine	Ph.D	2000	Biophysics
Johns Hopkins University – School of Medicine	Postdoctoral	2005	Structural Biology

A. Personal Statement

The focus of my research is on structural, mechanistic and functional aspects of enzyme activation/signal activation that play a role in biology of human disease such as cancer, parasitic infection and cardiovascular disease. I seek to understand how molecular events at the recognition level coordinate and trigger events in the cells. My work seeks to translate structural and mechanistic information on protein:protein interactions at the cytoplasmic level into preventive and therapeutic treatment for human disease. My background in biophysics with an emphasis in structural biology is the perfect match to carry out the proposed project. My training and experience in all aspects of the field allows me to lead with confidence the structural work of these projects. I have conducted, designed and directed projects using techniques of biochemistry, assay development, X-ray crystallography, cryoEM, SAXS, chemical biology, ITC, SPR, MS/MS and fluorescence. Recently, I have focused on designing immunotherapy interventions to make them more precise, off-the-shelf and effective for the treatment of solid tumors. Specifically, I am interested on dissecting the structural basis of pHLA recognition that allows to distinguish a neoantigen displayed in a cancer cell vs its wild type counterpart. I will use structure guided optimization of bispecifics and TCRs to explore and improve the signaling through the immunological synapse.
The main goal of my teaching, training and mentoring focuses on nurturing the development of independent, critical thinking and communications skills required for any career. I firmly believe that diversity is a crucial element in successful scientific teams and I strive to mentor, support and hire women, lgbt, underrepresented minorities and students from disadvantaged backgrounds.

Ongoing and recently completed projects that I would like to highlight include

1 R01 CA204345-01 (MPI) 6/01/16 – 5/31/21
Role: PI (Robert Casero is Lead PI)
Title: *Identification of novel spermine oxidase (SMOX) inhibitors as probes for an emerging chemoprevention target*

1 R01 GM136148-01A1 4/01/20 – 1/31/24
National Institute of Health
Role: Co-Investigator (Kane)
Title: *Regulation of P13K by PIK3IP1/TrIP*

1 R01 HL128743-01A1 (MPI) 4/01/16 – 3/31/21
NIH/NHLBI
Role: Co-Investigator (Multi-PI Amzel is Lead PI)

Title: *Calmodulin regulation of Na channels: from function and function to disease.*

1 R01 GM114250-06 (MPI) 1/07/21 – 5/31/25
NIH/GM
Role: Co-Investigator (Multi-PI N. Carrascol is Lead PI)
Title: *Mechanism of I^- transport by the Na^+/I^- symporter (NIS)*

B. Positions and Honors

Position and Employment

2017-present	Associate Professor, Department of Medicine, Oncology, Biophysics and Biophysical Chemistry, and Art as Applied to Medicine. JHU.
2016-present	Director of the Eukaryotic Tissue Culture Facility, Johns Hopkins University.
2011-2017	Assistant Professor, Department of Medicine, Oncology, Biophysics and Biophysical Chemistry, and Art as Applied to Medicine. JHU.
2010-2011	Instructor, Department of Oncology and Art as Applied to Medicine. JHU.
2006-2011	Instructor, Department of Biophysics and Biophysical Chemistry. JHU.
2002-2006	Research Associate, Department of Biophysics and Biophysical Chemistry. JHU.

Honors

2016-2018	NSLS-II Users' Executive Committee
2015-2017	Career Award GI SPORE
2013-2015	Alexander and Margaret Stewart Award
2015-2019	NCI SPORE Career Development Award
2011-2012	Emerging Women's Leadership Program. Office of Women in Science.
1994-1998	NSF graduate fellowship for minorities.
1998-1992	Fellowship. Comision de Investigaciones Cientificas de la Prov. de Bs Aires. CICPBA.
1987	Comision Argentino-Brasilena de Cs de Computacion Summer School. EBAI II. Award
1986	Universidad Nacional del Sur. Fellowship for undergraduates conducting research

Other Experience and Professional Memberships

2022	Reviewer, Macromolecular Structure &Function B Study Section NIH
2019	co-Lead of Workshop on Exploring New Science Frontiers at NSLS-II. BNL.
2017-2021	Associate Director of Conte Digestive Diseases Proteomics Core
2016-	NSLS-II Proposal Review Panel
2016	Beamline Advisory Team (BAT) for the NYX at Brookhaven National Laboratory- NSLSII
2013-2016	NSF Graduate Research Fellowship Program Evaluation-Panelist
2013-2016	Admissions Board of Graduate Program in Cellular and Molecular Medicine (CMM)- JHU
2013	Award for Creativity in Cancer Discovery Committee (JHU).
2013-2014	Nat. Def. Science and Eng. Graduate Fellowship P. (NDSEG) Evaluation panel.
2013-2014	Smart Defense Scholarship For Service Program Evaluation Panel.
2008-present	Reviewer of beamline time applications for Advanced Photon Source.
2010-present	Member, American Association for Cancer Research.
2003-2010	Member, American Chemical Society
1996-present	Member, Biophysical Society
1993-present	Member, American Crystallographic Association

C. Contribution to Science (86 peer reviewed publications, >126 PDB depositions)

http://www.ncbi.nlm.nih.gov/pubmed?cmd=Search&term=gabelli_sb&doptcmdl=DocSum
tinyurl.com/k4tmk4j2

1. Structural Basis of recognition of MHC-I presented neoantigens by antibodies. I aim to exploit the genetic aberrations that drive tumorigenesis to design personalized therapeutics by targeting the commonly mutated cancer driver genes which encode intracellular proteins, Mutated protein products derived from cancer driver genes can be processed and presented as peptides by human leukocyte antigen (HLA) molecules. We selected T cell receptor-mimic (TCRm) antibodies that can distinguish single amino acid differences between pHLA complexes derived from the protein products of cancer driver hotspot mutations and those from the native protein. We have grafted the TCRm antibodies into diabodies that bridge the T cell receptor to the HLA or converted to CAR T cell therapeutic formats. We have succeeded in designing an off-the-shelf protein therapeutic with the potential to be a immunotherapeutic for solid tumors targeting p53.

a. Miller MS, Douglass J, Hwang MS, Skora AD, Murphy M, Papadopoulos N, Kinzler KW, Vogelstein B, Zhou S, **Gabelli**[*]. An engineered antibody fragment targeting mutant β-catenin via Major Histocompatibility Complex I neoantigen presentation. J Biol Chem. 2019 Nov 5. pii: jbc.RA119.010251. doi: 10.1074/jbc.RA119.010251. PMID: 31690625; PubMed Central PMCID: PMC6916501
b. Han-Chung Hsie E, Wright KM, Douglas J, Hwang MS, Mog BJ, Pearlman AH, Paul S, DiNapoli SR, Konig MF, Wang Q, Schaefer A, Miller MS, Skora AD, Azurmendi PA, Murphy MB, Liu Q, Watson E, Li Y, Pardoll DM, Bettegowda C, Papadopoulos N, Kinzler KW, Vogelstein B, **Gabelli SB**[*]**,** Zhou S. Targeting a neoantigen derived from a common TP53 mutation. Science. 2021 Mar 5;371(6533):eabc8697. doi: 10.1126/science.abc8697. Epub 2021 Mar 1. PMID: 33649166
c. Paul S, Pearlman AH, Douglass J, Mog BJ, Han-Chung Hsie E, Hwang MS, DiNapoli SR, Konig MF, Brown PP, Wright KM, Sur S**, Gabelli SB**, Li Y, Ghiaur G, Pardoll DM, Papadopoulos, Bettegowda C, Kinzler KW, Zhou S, Vogelstein B. TCR beta chain-directed bispecific antibodies for the treatment of T cell cancers. Sci Transl Med. 2021 Mar 1:eabd3595. doi: 10.1126/scitranslmed.abd3595.. PMID: 33649188
d. Hwang MS, Miller MS, Thirawatananond P, Douglass J, Wright KM, Hsiue EH, Mog BJ, Aytenfisu TY, Murphy MB, Aitana Azurmendi P, Skora AD, Pearlman AH, Paul S, DiNapoli SR, Konig MF, Bettegowda C, Pardoll DM, Papadopoulos N, Kinzler KW, Vogelstein B, Zhou S, **Gabelli SB.** Structural engineering of chimeric antigen receptors targeting HLA-restricted neoantigens. Nat Commun. 2021 Sep 6;12(1):5271. doi: 10.1038/s41467-021-25605-4. PMID: 34489470

2. Structural Basis of mechanisms of activation and degradation of PI3K signaling pathway

Phosphoinositide 3-kinases are lipid kinases critical for insulin signaling. The oncogenic mechanism of activation has deemed PI3K as a molecular target for drug design. I have led the structural biology group that has determined seminal structures such as that of the wild type and the oncogenic mutant of PI3Kα. The latter gave the structural foundation for the design of drugs that target isoform and the mutant selectivity. The different complex structures suggest a mechanism by which the activation loop is inhibited in basal state. Recently, in my own lab, the determination of the structure of the complex with the substrate PIP_2 described the structural determinants of recognition of both p110α and p85α. This opened an alternative to the over-targeted ATP site. This work provides insight in the structural mechanism of activation and inhibition of an enzyme central to insulin signaling and cancer progression. The activating mutations of PI3Kα have different mechanism of activation. The combination of X-ray crystallography and small angle scattering (SAXS) is allowing us to create a dynamic picture of PI3Kα. I've been a senior and co-corresponding author since the first publication in 2007. My lab is working on designing therapeutics based on the mechanisms of degradation by targeting E3 ligases.

a. Miller MS, Maheshwari S, McRobb FM, Kinzler KW, Amzel LM, Vogelstein B, **Gabelli SB**. Identification of allosteric binding sites for PI3Kα oncogenic mutant specific inhibitor design. Bioorg Med Chem. 2017 Feb 15;25(4):1481-1486. doi: 10.1016/j.bmc.2017.01.012. Epub 2017 Jan 16.PMID:28129991. PMC5319926
b. Maheshwari S, Miller MS, O'Meally R, Cole RN, Amzel LM, **Gabelli SB**[*]**.** Kinetic and structural analyses reveal residues in phosphoinositide 3-kinase α that are critical for catalysis and substrate recognition J. Biol. Chem. jbc.M116.772426. doi:10.1074/jbc.M116.772426, PMID: 28676499; PMCID: PMC5566514

c. Chu N, Salguero AL, Liu AZ, Chen Z, Dempsey DR, Ficarro SB, Alexander WM, Marto JA, Li Y, Amzel LM, **Gabelli SB***, Cole PA. Akt Kinase Activation Mechanisms Revealed Using Protein Semisynthesis. Cell. 2018 Aug 9;174(4):897-907.e14. doi: 10.1016/j.cell.2018.07.003. Epub 2018 Aug 2. PMID: 30078705; PMCID: PMC6139374

d. Chakrabarti M, **Gabelli SB,** Amzel LM . Allosteric Activation of PI3Kα Results in Dynamic Access to Catalytically Competent Conformations. Structure. 2020. Structure. 2020 Apr 7;28(4):465-474.e5. doi: 10.1016/j.str.2020.01.010. Epub 2020 Feb 10. PubMed PMID: 32049032; PMCID: PMC805753

3. Versatility of the Nudix Enzymes

Throughout my career I have addressed phosphoryl transfer as it relates to regulation of disease. Early on, for my thesis work, I defined in Dr. Amzel lab, the structural basis of versatility of Nudix enzymes through the crystallographic determination of an enzyme of the family. This was part of a long-standing collaboration that I personally established with Dr. Maurice Bessman, ADPRase Nudix hydrolases are a superfamily of pyrophospho-hydrolases catalyzing the hydrolysis of a nucleoside diphosphate linked to another moiety. Some of the substrates are metabolites that require modulation and the enzymes control those levels. My work defines rules for identifying families according to their catalytic activity, tertiary structure, quaternary arrangement and phenotype. My publications describe the versatility of substrate recognition while keeping the elements of the chemistry conserved in families of nudix enzymes with substrates and different phenotypes. I have established substrate preferences and substrate involvement in metabolic pathways that has complemented the information of enzymes phenotype. This body of work defines the structure to function paradigm for the field of nudix enzymes. The different examples of nudix families provide archetypes to deconvolute catalysis, in the nudix motif, substrate recognition, in domains other than the nudix domain. Since becoming independent I have established new Nudix collaborations to distinguish my work from my mentor.

a. **Gabelli SB**, Bianchet MA, Bessman MJ, Amzel LM. The structure of ADP-ribose pyrophosphatase reveals the structural basis for the versatility of the Nudix family. Nat Struct Biol 2001 May;8(5):467-72. PMID: 11323725.

b. Duong-Ly KC, Woo HN, Dunn CA, Xu W, Babič A, Bessman MJ, Amzel LM, **Gabelli SB***. A UDP-X Diphosphatase from Streptococcus pneumoniae Hydrolyzes Precursors of Peptidoglycan Biosynthesis. PLoS One. 2013 May 15;8(5):e64241. doi: 10.1371/journal.pone.0064241. PMID: 23691178 PMCID: PMC3655063

c. Shumar SA, Kerr EW, Geldenhuys WJ, Montgomery GE, Fagone P, Thirawatananond P, Saavedra H, **Gabelli SB**, Leonardi R. Nudt19 is a renal CoA diphosphohydrolase with biochemical and regulatory properties that are distinct from the hepatic Nudt7 isoform.J Biol Chem. 2018 Mar 16;293(11):4134-4148. doi: 10.1074/jbc.RA117.001358. Epub 2018 Jan 29. PMID: 29378847 PMCID: PMC5857999

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4. Farnesyl Diphosphate Synthase as a Target for Parasitic Disease

Bisphosphonates, drugs used to treat bone resorption, have been shown to have an antiparasitic effect. In humans, they act by targeting farnesyl diphosphate synthase to lower the levels of protein prenylation. My work is focused in tailoring nitrogen-containing bisphosphonates to the parasitic enzymes of the isoprenoid pathway, minimizing the drug inhibitory effect in the host. I am using mutational analysis, enzymatic assays, isothermal calorimetry and X-ray crystallography to give the structural basis of specificity of the compounds. This project is a multisite collaboration with parasitologists and chemists at the Universities of Rio Grande do Norte, Brazil (Marcelo Silva Sousa), Georgia (Dr. R. Docampo), Urbana-Champaign (Dr. E. Oldfield) and Buenos Aires, Argentina (Dr. J.B. Rodriguez). As part of the project we have tailored the pharmacophore to increase specificity for the *T. cruzi, Leishmania major* and other protozoans *vs* that of humans. I started the project in *T. cruzi* when I was a postdoc with Dr. Amzel and now continue in *Leishmania* in my lab.

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5. Regulation of Channels and Exchangers by protein:protein interactions.

My work has defined the structural basis for the activation of Voltage gated sodium channels crucially expressed in cardiac and skeletal muscle. Our recent work on the structure and on the differential calcium modulation opens the road for physiological understanding, and mechanistically-coherent therapies. In particular, our data determined that many channelopathic mutations (Nav1.5 Brugada (BS); long QT syndromes (LQTS)) residing on the cytoplasmic domain, that give rise to numerous arrhythmias and myotonias, reduce apoCaM affinity, dislodge this binding partner, and thus modulate channels in ways that directly rationalize disease.

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