BIOGRAPHICAL SKETCH

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NAME: Lijia, Jia

eRA COMMONS USER NAME: LIJIA_JIA

POSITION TITLE: Research Assistant Professor/Facility Manager

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
The Agricultural University of Hebei, China	B.S.	06/2010	Plant Genetics
China Agricultural University, China	M.S.	3/2013	Plant Genetics and Breeding
University of Chinese Academy of Sciences, China	Ph.D.	07/2017	Structural Biology
Institute of Biophysics, Chinese Academy of Sciences, China	Postdoc	09/2019	Structural Biology; Epigenetics
Florida State University	Postdoc	01/2021	Structural Biology; Biochemistry
UT Health San Antonio (UTHSCSA)	Postdoc	01/2021-01/2022	Structural Biology; Biochemistry
UT Health San Antonio (UTHSCSA)	Research Assistant Professor/ Facility Manager	01/2022-Ongoing	Structural Biology; Biochemistry

A. Personal Statement

My long-term career goal has been to be a Cryo-EM facility Manager and Research Assistant Professor, with a particular interest in using single particle cryo-EM and eventually cryo-electron tomography to resolve large protein complexes. As an undergraduate and Master's student, I appreciated the value in studying how quantitative methods could inform biology, where I used statistical methods to map out how gene expression could influence mutant phenotypes in wheat production. It is also during this period of training that I became familiar with Maximum Likelihood methods, the main principle behind the popular Cryo-EM software Relion, which help push the resolution revolution in Cryo-EM protein structure determination. This computational background greatly helped me during my postdoctoral training at the Chinese Academy of Sciences to quickly learn the Cryo-EM softwares Relion, Cryosparc, and others and to resolve the structures of large protein complexes.

During my Ph.D., I acquired skillsets in protein biochemistry and structural biology using X-ray crystallography in the Institute of Genetics and Developmental Biology of Chinese Academy of Sciences, the leading research organization in China. During my Ph.D., I developed proficiency in cloning and molecular biology, protein purification, and X-ray crystallography - from crystal growth, data collection, and structure determination, and model building. In addition to experimentally-driven structure determination, I also implemented homology modeling (I-TASSER; Swiss-model; Robetta and Modeller), Molecular dynamics (Gromacs and VMD software), and molecular docking and virtual screening (Autodock and Autodock vina) – all of which helped me broaden my structural biology skills. After I finished my Ph.D. in 2017, I joined Ruiming Xu's group as a postdoctoral fellow, the director of the Institute of Biophysics of the Chinese Academy of Sciences, where we had two Titan Krios and one Talos Arctica for high resolution Cryo-EM structure determination. During this

time, I used single particle Cryo-EM to resolve the structure of a chromatin remodeler complex, which allowed me to familiarize myself with various Cryo-EM skillsets, including plunge freezing with a Vitrobot, screening and data collection, and data processing with Relion and Eman2. In 2019, in order to improve my Cryo-EM skills, I started a brief post-doc at Florida State University (FSU), as this institute has a long-standing influence in EM field. At FSU, I collaborated with Kenneth Taylor's and Scott Stagg's laboratories and gained proficiency in the Cryo-EM data collection software Leginon, as well as reinforced skillsets related to sample preparation, data collection and data processing. During my year at FSU, I was able to biochemically reconstitute a complex related to DNA replication and obtain a medium resolution structure by Cryo-EM.

These experiences have facilitated my move to UT Health Science Center at San Antonio (UTHSCSA) to start a brief post-doc before assisting in building the university's first cryo-EM facility, both under direction of Dr. Shaun Olsen, Director of Structural Biology Cores and a leading independent investigator in structural biology of ubiquitin signaling. In addition to my formal training in cryo-EM, I recently completed a 3 week embedded training at the National Center for Cryo-EM Access (NCCAT) in New York City to sharpen my cryo-EM skillsets (including sample preparation, microscope operation, data acquisition, and structure determination), and acquire facility manager training. As our cryo-EM facility opens in June 2022, I will be managing its Glacios cryo-TEM, equipped with a Falcon 4 direct electron detector, and a Selectris energy filter. In the interim period, I have set up and successfully utilized the Vitrobot, GPU computing, and data processing programs.

B. Positions and Honors

Positions and Employment

2017-2019 Postdoctoral Researcher, Institute of Biophysics, Chinese Academy of Sciences
2019-2020 Postdoctoral Associate, College of Medicine, Florida State University
2020-2022 Postdoctoral Fellow, Department of Biochemistry and Structural Biology, UTHSCSA
2022-Present Cryo-EM facility manager, UTHSCSA

Experience and Honors

2011 Selected to participate in training for QTL Mapping at the University of Zhejing
2015 Selected to participate in Phenix workshop at Tsinghua University
2017 Selected to participate in the training of Get Acquainted with Cryo-Electron Microscopy: Third Chinese Workshop for Structural Biologists in Tsinghua University
2018 Selected to participate in The 2018 K.H. Kuo CryoEM Tomography workshop & Symposium at the University of Zhejiang
2021 Three weeks embedded training at the National Center for Cryo-EM Access (NCCAT) for cryo-EM methodology, practice, and facility manager training

C. Contributions to Science

1. Early career

During my Masters, I mainly focused on using quantitative genetics to map candidate genes controlling wheat yield in the lab of Dr. Qixin Sun, the president of China Agricultural University. These works found that some elite gene sources could be derived from the Tibetan semi-wild wheat. Among them, several QTL-rich regions were mapped on 4 homologous groups. These discoveries expanded our genetic understanding of Tibetan semi-wild wheat, which will expand the repertoire of the genetic diversity of yield-related traits in modern wheat breeding program. Further analysis revealed that wheat Chromosome 4A and 4B harbor very stable genetic loci that control yield-related traits, independent of environmental changes, suggesting that these loci may be manipulated to breed out hardy wheat variants capable of growing well in different environments.

a) Liu G[#], **Jia LJ**[#], Lu LH, Qin DD, Zhang JP, Guan PF, Ni ZF, Yao YY, Sun QX, Peng HR. (2014) Mapping QTLs of yield-related traits using RIL population derived from common wheat and Tibetan semi-wild wheat. Theor Appl Genet. 127:2415–2432.

b) Guan P[#], Lu L[#], **Jia L[#],** KabirM R, Zhang J, Lan T, Zhao Y, Xin M, Hu Z, Yao Y, Ni Z, Sun Q, Peng H. (2018) Global QTL Analysis Identifies Genomic Regions on Chromosomes 4A and 4B Harboring Stable Loci for Yield Related Traits Across Different Environments in Wheat (Triticum aestivum L.) Front Plant Sci.

9:529.

2. Structural and functional characterization of protein enzymes

During my Ph.D., I utilized my training in plant sciences and computational biology to study the biochemical and structural aspects of Plant UDP-gal epimerase, N-Methyltransferase, vesicle-inducing protein, plastocyanin and salicylic acid biosynthesis regulators. I cloned all the four UDP-Gal epimerase found in the cytosol from Rice, and resolved their crystal structures. Structural comparison shows that the four UDP-Gal epimerases appear to have diverged over evolution. Using homology modeling, we identified key catalytic residues of Arabidopsis N-Methyltransferase, and confirmed biochemically that these sites contribute the enzyme activity and diversity (Li et al. Plant Physiol. 2017). Using homology modeling and molecular dynamics simulations, we identified the residues important for the interaction between plastocyanin and Cu; we confirmed biochemically that mutation of these residues contributes to the differential activtiies found in various plant species (Zhou et al. Plant Sci. 2018). My former research group is at present genetically following up on these observations to determine whether and how these key residues contribute to plant growth and development, discoveries that would allow for the development of more elite genetic resources.

a) Gao F, Chen B, Jiao J, **Jia LJ**, Liu CM. (2017) Two novel vesicle-inducing proteins in plastids 1 genes cloned and characterized in Urartu Triticum. Plos one. 12(1):e0170439.

b) Li W, Zhang FX, Wu RR, **Jia LJ**, Li GS, Guo YL, Liu CM, Wang GD. (2017) A novel N-Methyltransferase in Arabidopsis appears to feed a conserved pathway for nicotinate detoxification among land plants and is associated with lignin biosynthesis. Plant Physiol. 174(3):1492-1504.

c) Zhou XT, **Jia LJ**, Wang HY, Zhao P, Wang WY, Liu N, Song SW, Wu Y, Su L, Zhang J, Zhong NQ, Xia GX. (2018) The potato transcription factor StbZIP61 regulates dynamic biosynthesis of salicylic acid in defense against Phytophthora infestans infection. Plant J. 95(6):1055-1068.

d) Zhou XT, Wang F, Ma YP, **Jia LJ**, Liu N, Wang HY, Zhao P, Xia GX, Zhong NQ. (2018) Ectopic expression of SsPETE2, a plastocyanin from Suaeda salsa, improves plant tolerance to oxidative stress. Plant Sci. 268:1- 10.

3. Postdoctoral career – Using single particle Cryo-EM to resolve soluble protein complexes

During my postdoctoral training, I learned how to recombinantly overexpress proteins for structural determination in insect and mammal cells. I also became familiar with single particle Cryo-EM to expand my structural biology toolkit. My research projects early on have focused on studying dynamic complexes involved in chromatin biology – while at the Chinese Academy of Sciences, I studied a chromatin remodeler protein complex, and at FSU and UTHSA, I have worked on DNA lesion and replication complexes. For two of the three projects, I have collected Cryo-EM datasets and have been able to determine medium resolution structures of both these systems despite their conformational heterogeneity.

a) Lv Z, Cano KE, **Jia LJ**, Drag M, Huang TT, Olsen SK. (2022) Targeting SARS-CoV-2 proteases for COVID-19 antiviral development. *Frontiers in Chemistry*.

b) Yuan L, Gao F, Lv Z, Nayak D, Nayak A, Bury PDS, Cano KE, **Jia LJ**, Atligan FC, Oleinik N, Ogretmen B, El Oualid F, Wasmuth EV, Olsen SK. Structures of the bispecific Ubl activating enzyme Uba6 reveal novel catalytic and regulatory mechanisms. *IN REVIEW* (***2022***)

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BIOGRAPHICAL SKETCH

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NAME: ***Olsen, Shaun K.***

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

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 *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Rutgers University, New Brunswick, NJ	B.A.	05/2000	Biology
New York University, New York, NY	Ph.D.	05/2006	Biophysics/Biochemistry
Sloan Kettering Institute, New York, NY	Postdoctoral	07/2013	Biophysics/Biochemistry

A. Personal Statement

In broad terms, the research in my laboratory focuses on mechanisms of molecular recognition in protein-protein interactions and on the structural enzymology of proteins essential for cellular function. The majority of our efforts are focused on understanding how enzymes in the ubiquitin (Ub) conjugation cascade (E1, E2, and E3) function together to conjugate Ub to cellular proteins. Post-translational modification of proteins by Ub is a means of regulating fundamental cellular processes including cell cycle control, DNA repair, signal transduction, and immunity. The importance of understanding how the Ub system works is underscored by the fact that dysregulation of Ub signaling is implicated in a number of human disorders and that the pathway is a validated target for therapeutic intervention in cancer. To achieve our goals, we employ a multidisciplinary approach that includes X-ray crystallography, enzymology, a variety of biochemical and biophysical techniques, and cell-based functional assays in various eukaryotic systems to assess the biological importance of our structural, biochemical, and biophysical findings. More recently, my lab has expanded our structural toolkit, adopting single particle cryo-electron microscopy (cryo-EM) as a primarily methodology. We have now obtained several high and medium resolution structures of various complexes of the Ub pathway in the attached proposal that we believe can be further improved for publication with NCCAT GUP1 allocation.

B. Positions, Scientific Appointments, and Honors

Positions

2006-2008	Research Associate, Protein Research Group, RIKEN Genomic Sciences Center, Yokohama, Kanagawa, Japan
2008-2010	Adjunct Assistant Professor, Department of Chemistry & Biochemistry, Queens College (City University of New York, New York, NY
2008-2013	Postdoctoral Fellow, Structural Biology Program, Sloan-Kettering Institute, New York, NY
2013-2019	Assistant Professor, Department of Biochemistry & Molecular Biology, Medical University of South Carolina, Charleston, SC
2015-2020	Director, X-ray Crystallography Core, Medical University of South Carolina, Charleston, SC
2020	Associate Professor, Department of Biochemistry & Molecular Biology, Medical University of South Carolina, Charleston, SC
2020-pres	Director, Structural Biology Core Facilities, University of Texas Health at San Antonio, San Antonio, TX

2020-pres Co-Director, Drug Discovery and Structural Biology Shared Resource, Mays Cancer Center University of Texas Health at San Antonio, San Antonio, TX

2020-pres Associate Professor (tenured), Department of Biochemistry & Structural Biology, University of Texas Health at San Antonio, San Antonio, TX

Honors

1999 Phi Beta Kappa inductee
2000 Degree with Honors in the Liberal Arts, Rutgers University
2010-2012 Charles H. Revson Fellow, Sloan Kettering Institute
2010 Memorial Sloan Kettering Postdoctoral Researcher Award
2011 Blavatnik Award for Young Scientists (Finalist)
2017 MUSC High Impact Publication Award
2017 MUSC College of Graduate Studies Teacher of the Year Award
2018 MUSC College of Graduate Studies Teacher of the Year Award
2019 MUSC Developing Scholar Award
2020 Cancer Prevention & Research Institute of Texas- Rising Star Award
2021 UT STARs Faculty Award

C. Contributions to Science

Post-translational modification of proteins by ubiquitin, Nedd8, and SUMO (collectively termed Ubls) is a means of regulating fundamental cellular processes such as cell cycle control, signal transduction, and differentiation. Ubls are conjugated to proteins through the activity of an enzymatic cascade comprised of an E1 activating enzyme, an E2 conjugating enzyme, and in most instances, an E3 ligase. E1s function as gatekeepers of the conjugation cascades by specifically activating their cognate Ubl in two half-reactions involving adenylation and thioester bond formation. Despite a wealth of biochemical and structural information representing decades of research on E1s, the molecular mechanisms of E1-catalyzed adenylation and thioesterification of Ubls were unknown when I began working in this field, partially due to the unstable nature of key intermediates generated during catalysis. To solve this problem, I was involved in the development and application of semisynthetic protein-based inhibitors of Ubl E1s that enabled us to trap and determine structures of unstable intermediates formed in the two half-reactions catalyzed by E1s. These studies revealed that SUMO E1 has a single active site that is reconfigured for catalysis of adenylation or thioester bond formation via a series of complementary conformational changes in several regions of the E1. After adenylation, contacts to ATP/Mg are released, facilitating a dramatic 130 degree rotation of the E1 Cys domain and remodeling of several other structural elements that comprise the catalytic machinery of the adenylation active site. As a result, more than half of the residues that promote adenylation are replaced with residues that promote thioester bond formation, thereby toggling the catalytic competency of the active site. More recently, we obtained the first crystallographic snapshot of Ub E1 in which domain alternation and active site remodeling were observed. This study suggests that domain alternation and active site remodeling are intrinsic and interconnected structural features of Ub E1 and that the salient features of adenylation and thioester bond formation by Ub E1 is conserved across canonical Ubl E1s.

a. **Olsen SK,** Capili AD, Lu X, Tan DS, Lima CD. Active site remodeling accompanies thioester bond formation in SUMO E1. *Nature* **463**, 906-12 (2010) *[PMCID: 2866016]*
b. Lv Z, Yuan L, Atkison JH, Aldana-Masangkay G, Chen Y, **Olsen SK**. Domain Alternation and Active Site Remodeling Are Conserved Structural Features of Ubiquitin E1. *J. Biol. Chem*. **292**, 12089-12099 (2017) *[PMCID: 5519361]*
c. Lv Z, Yuan L, Atkison JH, Williams KM, Vega R, Sessions EH, Divlianska DB, Davies C, Chen Y, **Olsen SK**. Molecular mechanism of a covalent allosteric inhibitor of SUMO E1 activating enzyme. *Nat. Commun.* **9**,5145 (2018) *[PMCID: 6279746]*
d. Lv Z, Williams KM, Yuan L, Atkison JH, **Olsen SK**. Crystal structure of a human ubiquitin E1-ubiquitin complex reveals conserved functional elements essential for activity. *J. Biol. Chem*. **293**, 18337-18352 (2018) *[PMCID: 6254350]*

II. Once the E1~Ubl thioester intermediate has been generated, the next step in the Ubl conjugation cascade involves recruitment of an E2 enzyme followed by transfer of the Ubl from the E1 catalytic cysteine to the E2

catalytic cysteine. Although the structure of Nedd8 E1 in complex with its E2 had been determined prior to my entering this area of research, the E1 and E2 active sites were situated more than 20 Å away from each other and thus the conformational changes and contacts involved in bringing the E1and E2 active sites were unknown. Another unresolved issue was the basis by which a particular Ubl E1 achieves selectivity for its cognate E2(s) as opposed to E2s from other Ubl pathways. To gain insights into this process I developed a strategy for trapping E1 and E2 in a catalytically relevant conformation by specifically cross-linking their catalytic cysteine residues, a breakthrough that led to the first crystal structure of a Ub E1-E2 complex. The structure revealed a combinatorial mechanism for Ub E2 recruitment to Ub E1 that involves E2 contacts to two distinct domains of the E1 as well as conformational changes within the E1 that are required for the E1 and E2 active sites to come together during thioester transfer. More recently, we uncovered a new E1 binding mode for the E2 Ubc15 and determined that the intrinsically low level of E1-E2 thioester transfer activity of Ubc15 largely results from the presence of an acidic residue at its N-terminus that electrostatically clashes with an acidic patch on E1. Notably, the N-termini of many other Ub E2s are serine/threonine rich and we demonstrated that phosphorylation of these sites could serve as novel regulatory mechanism of Ub E2 activity.

a) **Olsen SK,** Lima CD. Structure of a ubiquitin E1-E2 complex: insights to E1-E2 thioester transfer. *Mol Cell.* **49**, 884-96 (2013) *[PMCID:* 3625138*]*

b) Lv Z, Rickman KA, Yuan L, Williams K, Selvam SP, Woosley AN, Howe, PH, Ogretmen B, Smogorzewska A, **Olsen SK**. *S. pombe* Uba1-Ubc15 structure reveals a novel regulatory mechanism of ubiquitin E2 activity. *Mol Cell.* **65**, 699-714 (2017) *[PMCID: 5319395]*

c) Williams KM, Que S, Atkison JH, Salazar-Arango S, Diehl JA, **Olsen SK**. Structural insights into E1 recognition and the ubiquitin-conjugating activity of the E2 enzyme Cdc34. *Nat. Commun.* **10**, 3296 (2019) *[PMCID: 6656757]*

d) Yuan L, Lv Z, Adams MJ, **Olsen SK**. Crystal structures of an E1-E2-ubiquitin thioester mimetic reveal molecular mechanisms of transthioesterification. *Nat. Commun.* **12**, 2370 (2021) *[PMCID: 8062481]*

III. The E2~Ub intermediate resulting from E1-E2 thioester transfer interacts with members of three different families of Ub E3 ligases (RING, HECT, and RING-in-between-RING (RBR)) that catalyze Ub conjugation to target proteins by distinct mechanisms. RBR E3s are a distinct class of Ub E3 ligases that function through a RING/HECT hybrid mechanism in which the RBR RING1 domain initially recruits the E2~Ub thioester intermediate, similar to canonical RING E3s. However, rather than facilitating Ub discharge from E2~Ub onto target protein lysine residues directly like a canonical RING E3, E2~Ub binding to the RING1 domain of RBR E2s is followed by thioester transfer of Ub to a catalytic cysteine residue in the RING2 domain similar to HECT E3s. A fundamental question that arises from these observations is how RBRs prevent Ub discharge to lysine residues upon E2~Ub to the RING1 domain, despite RING1 strongly resembling a canonical RING E3. We recently determined the crystal structure of the RBR E3, HHARI, in complex with a UbcH7~Ub thioester mimetic. The structure revealed mechanistically important UbcH7~Ub-induced conformational changes in the RING1 and UBA-like domains of HHARI that play a key role in determining the specificity of this E2/E3 pair, as well as in promoting recruitment of UbcH7~Ub in the 'open' conformation. Overall, our structural and biochemical studies indicate that HHARI ensures transfer of Ub from E2 to the RING2 catalytic cysteine as opposed to discharge from E2 directly to lysine residues upon RING1 binding in at least three ways: 1) by evolving a mechanism to specifically recruit an E2 that solely performs transthiolation (UbcH7), 2) by harboring a loop insertion in the RING1 domain (unique to RBR E3s) that is involved in determining specificity of HHARI for UbcH7 and is incompatible with the UbcH7~Ub binding in the 'closed' conformation primed for Ub discharge to lysine residues, and 3) contacts between Ub and the UBA-like domain that promote recruitment of UbcH7~Ub in the inactive 'open' conformation.

a) Yuan L, Lv Z, Atkison JH, **Olsen SK**. Structural insights into the mechanism and E2 specificity of the RBR E3 ubiquitin ligase HHARI. *Nat Commun* **8**, 211 (2017) *[PMCID: 5548887]*

IV. The emergence of severe acute respiratory syndrome (SARS-CoV-2) in 2019 marked the third occurrence of a highly pathogenic coronavirus in the human population since 2003. As the death toll surpasses 4 million globally and economic losses continue, designing potential drugs that could curtail infection and disease progression is critical. Viral papain-like cysteine protease (PLpro, NSP3) is essential for SARS-CoV-2 replication and represents a promising target for the development of antiviral drugs. To address the need for

COVID-19 antiviral therapies, we used a combinatorial substrate library and performed comprehensive activity profiling of SARS-CoV-2 PLpro. On the scaffold of the best hits from positional scanning, we designed optimal fluorogenic substrates and irreversible inhibitors with a high degree of selectivity for SARS PLpro. We determined crystal structures of two of these inhibitors in complex with SARS-CoV-2 PLpro that reveals their inhibitory mechanisms and provides a molecular basis for the observed substrate specificity profiles. We demonstrate that SARS-CoV-2 PLpro harbors deISGylating activity similar to SARS-CoV-1 PLpro but its ability to hydrolyze K48-linked Ub chains is diminished, which our sequence and structure analysis provides a basis for. Together, this work has revealed the molecular rules governing PLpro substrate specificity and provides a framework for development of inhibitors with potential therapeutic value or drug repurposing. In later work, we identified a molecular sensor within the S1 Ub-binding site of PLpro that serves as a key determinant of substrate specificity. Amino-acid variations within the S1 sensor specifically alter cleavage of Ub substrates but not of the Ubl ISG15. Significantly, a variant of concern associated with immune evasion carries a mutation in the S1 sensor and this mutation enhances PLpro activity on Ub substrates. Collectively, our data identify the S1 molecular sensor as a potential hotspot of variability that could dramatically alter host antiviral immune responses to newly emerging SARS-CoV-2 lineages.

a) Rut W, Lv Z, Zmudzinski M, Patchett S, Nayak D, Snipas SJ, El Oualid F, Huang TT, Bekes M, Drag M, **Olsen SK**. Activity profiling and crystal structures of inhibitor-bound SARS-CoV-2 papain-like protease: A framework for anti-COVID-19 drug design. *Science Advances* **6**,eabd4596 (2020) *[PMCID: 7567588]*

b) Patchett S, Lv Z, Rut W, Bekes M, **Olsen SK***, Huang TT. A molecular sensor determines the ubiquitin substrate specificity of SARS-CoV-2 papain-like protease. *Cell Reports* **36**, 109754 (2021) *[PMCID: 8423903]*
*co-corresponding author

c) Lv Z, Cano KE, Jia L, Drag M, Huang TT, Olsen SK. Targeting SARS-CoV-2 proteases for COVID-19 antiviral development. *Frontiers in Chemistry* **9**, 819165 (2022) *[PMCID: 8850931]*

V. Fibroblast growth factors play an essential role in human biology as regulators of embryonic development, homeostasis and regenerative processes. The twenty-two mammalian FGFs elicit their distinct biological effects by binding to and activating a unique subset of FGF receptor tyrosine kinases (FGFR1-4) at the cell surface. Alternative splicing of FGFs and FGFRs generates an additional level of sequence diversity, which in turn ultimately determines specificity in the FGF-FGFR system. A tissue-specific alternative splicing event in Ig domain 3 of FGFR1-3 results in the expression of epithelial FGFRb isoforms and mesenchymal FGFRc isoforms, and allows for directional epithelial-mesenchymal signaling which is required for organogenesis. To better understand the basis for molecular recognition in FGF-FGFR interactions and how alternative splicing governs specificity in these interactions, I structurally and biochemically characterized a selected set of FGF-FGFR pairs. The results of these studies revealed the basis by which FGF8 achieves exquisite specificity for the 'c' isoforms of FGFR and for how alternative splicing at the N-terminus of FGF8 regulates the organizing potential of this protein in the brain. I also determined the molecular basis by which FGF1 functions as a 'pan' FGFR ligand due to its ability to activate all FGFRs. These studies revealed that FGF1 exhibits a remarkable degree of structural plasticity that equips this protein with the adaptability required to engage in contacts with the distinct interaction surfaces presented to it by the repertoire of FGFRs present in cells. Together, this work answered a number of longstanding questions in the FGF field and contributed to the transformation of FGF signaling into one of the foremost structurally understood ligand-receptor systems among receptor tyrosine kinases.

a. **Olsen SK**, Bromleigh C, Ibrahimi OA, Eliseenkova AV, Zhang F, Linhardt RJ, Joyner AL, Mohammadi, M. Structural Basis By Which Alternative Splicing Modulates the Biological Activity of FGF8 in the Brain. Genes Dev. **20**, 185-98. (2006) *[PMCID: 1356110]*

b. **Olsen SK**, Ibrahimi OA, Raucci A, Zhang F, Eliseenkova AV, Yayon A, Basilico C, Linhardt RJ, Schlessinger J, Mohammadi M. Insights into the molecular basis for fibroblast growth factor receptor autoinhibition and ligand-binding promiscuity. Proc. Natl. Acad. Sci. U S A. **101**, 935-40 (2004) *[PMCID: 327120]*

c. **Olsen SK**, Garbi M, Zampieri N, Eliseenkova AV, Ornitz DM, Goldfarb M, Mohammadi, M. Fibroblast growth factor (FGF) homologous factors share structural but not functional homology with FGFs. J. Biol. Chem. **278**, 34226-36 (2003) *[PMCID:12815063]*

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D. Additional Information: Research Support and/or Scholastic Performance

Ongoing

1R01GM115568 09/01/2020 – 08/31/2024 Olsen (PI)

Structural Biology of the Ubiquitin Conjugation System- The research in this proposal aims to establish the rules governing molecular recognition and promiscuity across Ub E1-E2 and E2-RING-in-between-RING E3 ligase interactions.

Role: PI

1R01GM128731 04/15/2019 – 02/28/2023 Olsen (PI)

Structure and function of the essential cell cycle regulator Cdc34- The goal of this project is to elucidate the molecular mechanisms by which the three enzymes E1, Cdc34, and SCF E3 function together as essential regulators of the cell cycle by specifically assembling Lys48 polyubiquitin chains on target proteins.

Role: PI

RR200030 09/01/2020 – 08/31/2025 Olsen (PI)

Recruitment of Rising Stars Investigator- This faculty recruitment award is a startup package that provides general support to the Olsen laboratory over a 5-year period, including salaries for laboratory personnel, supplies, equipment purchase, equipment maintenance and repair, facility renovations, secretarial support, core facility access fees, and travel.

Role: PI

P30 CA054174 08/01/2020-7/31/2025 Mesa (PI)

Mays Cancer Center at UT Health San Antonio. This cancer center support grant provides research core and program infrastructure support to members of the cancer center for the conduct of their cancer research.

Role: co-Leader, DDSBSR, CCSG Core 005

SA PPT 2021 01/01/2021-12/31/2023 Bohmann (PI)

HSC-SA PARTNERSHIP PRECISION THERAPEUTIC $25,000

Development of Therapies for the Henipaviruses Hendra and Nipah- The goal of this project is to develop new antiviral small-molecules by targeting the attachment glycoprotein G
of Nipah and Hendra virus.

Role: co-investigator

PRMRP Ref# PR211252 01/01/2022 – 01/01/2024 (Bohmann, PI)

DoD $50,000

Development of Antiviral Therapies against Nipah and Hendra Viruses- The goal of this project is to determine whether novel compounds from a custom library of small molecules affect Nipah and/or Hendra virus infection in vitro, by targeting the viral F Fusion protein.

Role: co-investigator