BIOGRAPHICAL SKETCH

NAME: Feigon, Juli

eRA COMMONS USER NAME (credential, e.g., agency login): FEIGON2

POSITION TITLE: Distinguished Professor of Biochemistry

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Occidental College, Los Angeles, CA	B.A.	06/1976	Chemistry
University of California, San Diego	M.S.	06/1978	Chemistry
University of California, San Diego	Ph.D.	06/1982	Chemistry
Massachusetts Institute of Technology, Boston	Postdoc	10/1985	Biology

A. Personal Statement

My research interests are in structural biology of nucleic acids and their complexes. Historically, my laboratory pioneered the application of macromolecular NMR spectroscopy to the study of DNA and RNA structure, folding, and interactions with cations, drugs, and proteins. My laboratory published the first structures of DNA triplexes [1,2], quadruplexes [3], and aptamers [4], and our work has provided fundamental insights into DNA A-tract and protein induced bending, cation interactions with DNA, Hoogsteen base pairs, and drug binding to DNA. Over the past two decades we have made major contributions in understanding RNA folding and function, including studies of RNA aptamers [5], ribozymes, and riboswitches [6-8], and recognition of RNA by proteins [9-11]. We solved the first NMR structure of a riboswitch and set the standard for high-resolution RNA structures determined by NMR [6, 7]. For all of this work, we developed new NMR methods and applications for studying nucleic acids structure and dynamics, including assignments and detecting cation interactions. Our work has combined structural and functional studies of RNA-protein complexes to reveal essential determinants of protein recognition of single stranded and of double stranded RNA by RRMs [9-11] and dsRBDs, respectively. We have made major contributions to understanding the structure, function, processing, and assembly of H/ACA RNPs, RNase III, and telomerase [9, 11-19]. We have also done seminal work on the structure and interactions of UBA and Ubl domains found in the DNA repair protein human homologue of Rad23 (HHR23A), including determining the first structures of a UBA domain and a complex of a Ubl domain with the S5a subunit of the proteasome.

Our current work employs an integrative structural biology approach combining NMR spectroscopy, X-ray crystallography, and electron microscopy (EM) along with biochemistry to study structure, dynamics, and function of non-coding RNA and RNA-protein complexes, in particular 7SK RNP and telomerase. For the past decade, a major focus of the laboratory has been on telomerase structure and function. We have determined solution NMR and X-ray crystal structures of RNA and RNA-protein domains of human and *Tetrahymena* telomerase and investigated their dynamics by NMR [9, 11-14]. Our laboratory reported the first structure of a telomerase holoenzyme, by negative stain EM at 25 Å resolution [16], and subsequently by cryo-EM at 9Å [17] and recently at 4.8 Å [19] resolution.

I was the first female assistant professor in my department, and I consider the training of my lab members (postdocs, graduate students, undergraduates) as an enduring contribution to science and society. The majority of my postdocs have gone on to academic positions, e.g. Frederic Allain (ETH), Sam Butcher (U. Wisc Madison), Carla Theimer (Maria College), Mahavir Singh (Indian Institute of Science), Qi Zhang (UNC), and most recently Jiansen Jiang (NIH) to name a few; others to positions in biotechnology companies; and graduate student Roman Macaya is currently Ambassador to the US from Costa Rica after a career in biotech. Among other contributions to the scientific community beyond reviewing papers and grants and serving on journal editorial boards, I have been selected by my peers as co-organizer of the RNA Society meeting (twice), the Keystone Meeting on Frontiers of NMR in Molecular Biology (twice), and Nucleic Acids Gordon Conference. I was a member of the advisory board for the then newly formed RCSB PDB (1999), which serves as a structural biology resource for the worldwide scientific community, for 7 years and on the NMR task force for the PDB, for a total of 9 years, where I represented the nucleic acids community.

B. Positions and Honors

Positions and Employment

1976-1982 Teaching Assistant, Research Assistant, UCSD
1982 Postgraduate Research Chemist, UCSD
1982-1985 Damon Runyon-Walter Winchell Cancer Fund Postdoctoral Fellow, MIT
1985-1990 Assistant Professor, Department of Chemistry and Biochemistry, UCLA
1990-1994 Associate Professor, Department of Chemistry and Biochemistry, UCLA
1994-2013 Professor, Department of Chemistry and Biochemistry, UCLA
2013- Distinguished Professor, Department of Chemistry and Biochemistry, UCLA
1990- Member, Molecular Biology Institute, UCLA
2004- Member, UCLA-DOE Institute of Genomics and Proteomics

Other Experience and Professional Memberships

1981- Member, Biophysical Society
1996-1999 Member, Science Public Policy Committee, Biophysical Society
1997- Member, RNA Society
2007- Member, American Association for Biochemistry and Molecular Biology
2007- Council Member, International Society of Magnetic Resonance (ISMAR)
2009- Member, National Academy of Sciences (NAS)

Editorial service for scientific journals

1993-2001 Editorial Advisory Board Member, *Biochemistry*
1996-2004 Editorial Advisory Board Member, *Chemistry & Biology*
1998-2010 Editorial Advisory Board Member, *Journal of Magnetic Resonance*
2001- Section Head: *Faculty of 1000 Biology*, Structure: RNA
2005- Editorial Advisory Board member*, Journal of Biomolecular NMR*
2007- Editorial Advisory Board member, *Biomolecular NMR Assignments*
2007- Associate Editor, *Journal of RNA Biology*
2009- Advisory Board Member: *Faculty of 1000 Biology Reports*

Service as reviewer and meeting organizer

1988 NIH review panel for Shared Instrumental Program
1992 Site visit, Initiative in Biomolecular Engineering, Dept. of Energy, Berkeley, CA
1995 Site visit, NIH Special Review Section, Yale University
1995 Co-Chair (with Douglas Turner), Nucleic Acids Gordon Conference
1995-2001 NMRFAM Scientific Advisory Committee, University of Wisconsin
1996 Chair, Molecular Biophysics Subgroup Meeting, Biophysical Society
1997 Ad Hoc Member, NIH AIDS Institute (AARD) Study Section
1999-2002 NMR Task Force for the new Protein Data Bank (PDB), member
1999-2006 Research Collaboratory for Structural Bioinformatics (RCSB) PDB Advisory Board member
2001 NIH Shared Instrument Grant Special Study Section, Rockville, MD
2001 NIH Center for Scientific Review Special Study Section
2002 Co-Chair, RNA Society Meeting, Madison, WI
2003 Organizer for 2003 Seaborg Symposium, UCLA, Los Angeles, CA
2005 Co-organizer for 'Frontiers of NMR in Molecular Biology' Keystone Symposia, Banff
2005-2009 RCSB Protein Data Bank NMR Task Force member
2005-now Advisory Committee member of the MIT-Harvard Center for Magnetic Resonance
2007 Co-organizer for 'Frontiers of NMR in Molecular Biology' Keystone Symposia, Snowbird, UT
2008 NSF Special Review Panel
2008 National Advisory Committee member for 23rd International Conference on Magnetic Resonance in Biological Systems Meeting (ICMRBS), San Diego, CA
2009,-10,-15 Reviewer, Howard Hughes Medical Institute Investigators
2010 Co-Chair, RNA Society Meeting, Seattle, WA
2013 NSF Special Review Panel member
2013-now Scientific Advisory Board member for the Center for HIV RNA Studies (CRNA) (P41)
2014 NIH Special Study Section member
2018 Alexander Hollaender Award Selection Committee member

Honors and Awards

1975 Phi Beta Kappa
1982-1985 Damon Runyon-Walter Winchell Cancer Fund Postdoctoral Fellowship
1984 National Research Service Award, National Institute of General Medical Sciences, NIH

1985-1986	Dupont Young Faculty Award
1989-1994	Presidential Young Investigator, National Science Foundation
1990	Camille and Henry Dreyfus Teacher/Scholar Award
1992	Glenn T. Seaborg Research Award
1993, 2009	Herbert Newby McCoy Research Award
2002	Elected Fellow of the American Association for the Advancement of Science (AAAS)
2009	Elected Member, National Academy of Sciences
2014-2019	Christopher Foote Term Chair
2017	Dorothy Crowfoot Hodgkin award of the Protein Society

C. Contributions to Science (with emphasis on recent plus seminal contributions with current impact)

Complete publication list: (175 total)
https://www.ncbi.nlm.nih.gov/sites/myncbi/juli.feigon.1/bibliography/40335254/public/?sort=date&direction=ascending

1. Structural studies of DNA triplexes, quadruplexes, and aptamers. My laboratory pioneered the application of multidimensional NMR spectroscopy to the study of DNA and later RNA. Early work from my laboratory on Z-DNA, drug-DNA complexes, DNA triplexes [1,2] quadruplexes [3,4], and aptamers [4] was seminal in defining the conformational variability of DNA. We determined the first structure of a DNA triplex and of a DNA quadruplex (prior to crystal structures). Our work on DNA triplexes characterized their sequence requirements, stability, specificity, and structure. More recently, we characterized naturally occurring RNA triplexes identified for the first time in a telomerase pseudoknot [11] and since then in a number of different RNAs, including riboswitches [8]. RNA triplexes are increasingly recognized as important in biology. Our landmark 1992 structural study of DNA quadruplexes formed by *Oxytricha* telomere repeats [3] was seminal to the now burgeoning fields of G-quadruplex targeted anticancer and telomerase inhibiting drugs and DNA nanostructures. We also determined the structure of a thrombin binding DNA aptamer, which turned out to be a quadruplex with 2 G-quartets [4]. The thrombin binding aptamer has been extensively investigated as a potential thrombin inhibitor. Also of note for the NMR field is that for both the telomere repeat quadruplex and the thrombin binding aptamer, crystal structures published about the same time had a different topology, and in both cases the NMR structure was correct, establishing my laboratory as a leader in the field. All of these papers are still being cited.

1) P. Rajagopal and J. Feigon: “Triple strand formation in the homopurine:homopyrimidine DNA oligonucleotides d(GA)$_4$ and d(TC)$_4$”, *Nature* **339**, 637-640 (1989).
2) V. Sklenář and J. Feigon: “Formation of a stable triplex from a single DNA strand”, *Nature* **345**, 836-838 (1990).
3) F.W. Smith and J. Feigon: “Quadruplex structure of telomeric DNA oligonucleotides”, *Nature* **356**, 164-168 (1992).
4) R.F. Macaya, P. Schultze, F.W. Smith, J.A. Roe, and J. Feigon: “Thrombin-binding DNA aptamer forms a unimolecular quadruplex structure in solution”, *Proc. Natl. Acad. Sci. USA* **90**, 3745-3749 (1993). PMCID: PMC46378.

2. RNA aptamers, riboswitches, and ribozymes. Aptamer is a name coined by the Szostak laboratory for RNAs that have been selected in vitro for binding to specific ligands or performing specific chemistry. We determined the NMR structure of the 36 nucleotide ATP-binding aptamer, the first aptamer selected for binding to a biological co-factor, in complex with AMP [5]. This was one of the first RNA aptamers structures to be determined. The structure completely explained the sequence conservation of the ATP-binding aptamer and revealed that RNA aptamers form binding pockets around their ligands using a combination of well-known structural motifs and unanticipated interactions. For this and other studies of RNAs such as the hairpin ribozyme we developed new NMR pulse sequences for obtaining assignments using ^{13}C,^{15}N-labeled RNA and optimized methods for structure determination. Subsequently, naturally occurring aptamers were discovered as the metabolite or ligand-binding domain of riboswitches. Riboswitches are non-translated RNAs, most commonly found in the 5’-UTR of bacterial genes, that change conformation upon binding a ligand, resulting in downstream conformational changes that turn on or off transcription or translation. Our laboratory determined the first NMR structure of a riboswitch aptamer, from the preQ1(I) riboswitch [6]. A subsequent rigorous comparison to a crystal structure of the same riboswitch using RDCs revealed that small differences between the solution and crystal structures in the upper half of the riboswitch were real and were due to the presence of Ca^{2+} in the crystal structure [7]. This comparison also showed that by using sufficient NOE and RDC restraints RNA structures determined by NMR are comparable to crystal structures, even for determining new interactions like our ‘A-amino kissing’ motif. More recently we determined the structure of a larger class II preQ1 riboswitch, which has a different tertiary fold and mode of recognition of preQ1 than the class I riboswitch [8]. This structure also contains a triple-helical region similar to the telomerase pseudoknot [12].

5) T. Dieckmann, E. Suzuki, G.K. Nakamura, and J. Feigon: “Solution structure of an ATP-binding RNA aptamer reveals a novel fold”, *RNA* **2**, 628-640 (1996). PMCID: PMC1369402.
6) M. Kang, R.D. Peterson, and J. Feigon: “Structural insights into riboswitch control of the biosynthesis of queuosine, a modified nucleotide found in the anticodon of tRNA”, *Mol. Cell,* **33**, 784-790 (2009).
7) Q. Zhang, M. Kang, R.D. Peterson, and J. Feigon: “Comparison of solution and crystal structure of preQ1 riboswitch reveals calcium-induced changes in conformation and dynamics”, *J. Am. Chem. Soc.* **133**, 5190-5193 (2011). PMCID: PMC3085290
8) M. Kang, C.D. Eichhorn, and J. Feigon, “Structural determinants for ligand capture by a class II preQ1 riboswitch”, *Proc. Natl. Acad. Sci. U.S.A.,* **111**, E663-671 (2014). PMCID: PMC3926045.

3. Structure and function of LARP7 proteins The La and the La-related protein (LARP) superfamily is diverse class of RNA binding proteins involved in RNA processing, folding, and function for diverse RNA targets, including tRNAs, snRNAs, snoRNAs, 7SK lncRNA and telomerase RNA. The *Tetrahymena* telomerase holoenzyme LARP7 protein p65 facilitates assembly of TER with TERT. Biochemical and FRET studies established that p65 contains a La module (La motif + RRM) that binds the 3’UUU of TER and a C-terminal domain (CTD), of no apparent known motif, that was necessary and sufficient for hierarchal assembly. Using NMR and X-ray crystallography, we identified p65 CTD as a new type of RNA recognition motif (named xRRM) with features unique from other RRMs [9]. The structure of a complex of p65 xRRM with TER stem 4 revealed that the xRRM bends TER stem-loop 4 by 105°, a conformational change in TER required for assembly in vivo [9]. Based on the structure and sequence analysis, we predicted that the mode of binding, which combines recognition of both unpaired and base-paired nts, would be common to other LARP7 proteins [9,10]. The 7SK RNP is a dynamic assembly that regulates eukaryotic transcription at the transition from initial transcribing to the elongation complex. The 7SK lncRNA forms a core RNP with methylphosphate capping enzyme (MePCE) and Larp7. Our solution NMR structure of human Larp7 CTD confirmed that it is an xRRM with some distinctive features, and we identified its binding site on the 3’ terminal hairpin of 7SK RNA and RNA nts important for high affinity binding [11]. Our X-ray crystal structure of human Larp7 xRRM in complex with the 7SK loop 4 (PDB 6D12) is the first structure of a 7SK RNA-protein complex, providing insights into assembly and function (*Proc. Natl. Acad. Sci,* in minor revision).

9) M. Singh, Z. Wang, B.-K. Koo, A. Patel, D. Cascio, K. Collins, and J. Feigon: “Structural basis for telomerase RNA recognition and RNP assembly by the holoenzyme La family protein p65”, *Mol Cell* **47**, 16-26 (2012). PMCID: PMC3398246.
10) M. Singh, C.P. Choi, and J. Feigon: “xRRM: A new class of RRM found in the telomerase La family protein p65”, *RNA Biol.* **10**, 353-359 (2013). PMCID: PMC3672277.
11) C.D. Eichhorn, R. Chug and J. Feigon “hLARP7 C-terminal domain contains an xRRM that binds the 3’ hairpin of 7SK RNA”, *Nucleic Acids Res.* **44**, 9977-9989 (2016). PMCID: PMC5175362.

4. Telomerase RNA structure and function For more than a decade, a major focus of my laboratory has been on determining the structural basis for telomerase holoenzyme activity and assembly. Telomerase is an RNP that helps maintain the DNA in telomeres, the protein-DNA complexes at the physical ends of chromosomes, by processive synthesis of the G-strand telomere repeat, d(TTAGGG) in vertebrates. Telomerase contains a specialized telomerase reverse transcriptase (TERT), an essential telomerase RNA (TER) that contains a template for DNA synthesis and other elements essential for function, and various accessory proteins. Our initial studies focused on structure-function studies of TER, and almost all TER domain structures solved to date are from my lab. Our seminal study of the human TER minimal pseudoknot revealed it contained conserved base triples that formed a triple-helix essential for function [12]. We have determined NMR structures of the minimal pseudoknot from yeast *K. lactis* [14], *Tetrahymena* [17], and the teleost fish medaka [15], which contains the smallest vertebrate TER. These structures show that all contain a triple-helical region, and functional studies showed that formation of the triples is important for activity in vitro and telomere length maintenance in vivo. Another major achievement was a model of the complete template/pseudoknot domain based on NMR structures, dynamics studies, and activity assays [13]. This model showed that a region of TER adjacent to the minimal pseudoknot, which contains a 5 nt bulge conserved in location but not sequence, bends the helix by ~90° and determines the overall topology of the template/pseudoknot domain. We showed that this topology is conserved in vertebrates from fish to human [15]. Based on the TER location in our 9Å cryoEM structure of Tetrahymena telomerase we were able to model the human telomerase TERT-TER catalytic core [15]. Our studies have defined the roles of TER domains in telomerase biogenesis, assembly, and activity.

12) C.A. Theimer, C.A. Blois, and J. Feigon: “Structure of the human telomerase RNA pseudoknot reveals conserved tertiary interactions essential for function”, *Mol. Cell* **17**, 671-682 (2005).
13) Q. Zhang, N.-K. Kim, R.D. Peterson, Z. Wang, and J. Feigon: “Structurally conserved five nucleotide bulge determines the overall topology of the core domain of human telomerase RNA”, *Proc. Natl. Acad. Sci. USA*

107, 18761-18768 (2010). PMCID: PMC2973926
14) D.D. Cash, O. Cohen-Zontag, N.-K. Kim, K. Shefer, Y. Brown, N.B. Ulyanov, Y. Tzfati, and J. Feigon, "Pyrimidine motif triple helix in the *Kluyveromyces lactis* telomerase RNA pseudoknot is essential for function in vivo", *Proc. Natl. Acad. Sci. USA* **110**, 10970-10975 (2013). PMCID: PMC3704002.
15) Y. Wang, J.D. Yesselman, Q. Zhang, M. Kang, and J. Feigon, "Structural conservation in the template/pseudoknot domain of vertebrate telomerase RNA from teleost fish to human", *Proc. Natl. Acad. Sci. USA*, **13**(35):E5125-34 (2016). PMCID: PMC5024593.

5. Tetrahymena telomerase holoenzyme We have published three landmark papers on telomerase holoenzyme structure, each of which has provided unanticipated insights into function. In 2013, we published the first and long awaited structure of a telomerase holoenzyme, from *Tetrahymena*, determined by negative stain electron microscopy at 25Å resolution. We localized all but one of the 7 known proteins and the telomerase RNA (TER) by affinity labeling and modeling and determined the overall architecture of the enzyme [16]. We discovered that p50, a protein previously thought to be sub-stoichiometric, was essential to the processivity enhancement of telomeric DNA binding accessory protein Teb1. In 2015, we reported the first cryoEM structure of telomerase, at ~9Å resolution, along with the NMR structure of the TER pseudoknot, crystal structures of p19 and p45C, and we identified new subunits Teb2 and Teb3 by mass spectrometry and modeling [17] that form a heterotrimeric complex with Teb1 (TEB). The p19 and p45N crystal structures and cryoEM map revealed that subunits p75-p45-p19 were homologues of the telomere associated CST complex found in humans and yeasts. Fitting of NMR and crystal structures of subdomains and homology models revealed the path of TER on TERT and the structural basis of 5' template boundary definition. TEB is paralogous to the single-strand DNA binding Replication Protein A (RPA), which plays central roles in DNA replication and repair. Remarkably, we found that Teb2 and Teb3 are shared subunits with Tetrahymena RPA (Rpa1-Teb2-Teb3) [18]. We recently reported the 4.8Å cryoEM structure of active Tetrahymena telomerase with telomeric DNA [19]. This study provides the first complete model of TERT and the TERT-TER catalytic core, revealing a unique interlocked TERT-TER structure, a new structural feature (TRAP) of TERT, a re-interpretation of the role of TERT TEN, the role of template flanking TER sequences during telomeric DNA synthesis, how the template-DNA duplex interacts with the active site, how the DNA exits the active site and binds TEB, and how p50 and TEB (homologous to human telomere interacting proteins) interact with TERT.

16) J. Jiang, E.J. Miracco, K. Hong, B. Eckert, H. Chan, D.D. Cash, B. Min, Z. H. Zhou, K. Collins, and J. Feigon, "The architecture of *Tetrahymena* telomerase holoenzyme", *Nature*, **496**, 187-192 (2013). PMCID: PMC3817743.
17) J. Jiang, H. Chan, D. D. Cash, E. J. Miracco, R. R. Ogorzalek Loo, H. E. Upton, D. Cascio, R. O'Brien Johnson, K. Collins, J. A. Loo, Z. H. Zhou, and J. Feigon, "Structure of Tetrahymena telomerase reveals previously unknown subunits, functions, and interactions", *Science* **350**, aab4070 (2015). PMCID: PMC4687456
18) H. E. Upton, H. Chan, J. Feigon, and K. Collins, "Shared Subunits of Tetrahymena Telomerase Holoenzyme and Replication Protein A Have Different Functions in Different Cellular Complexes", *J. Biol. Chem.*, **292**, 217-228 (2017). PMCID: PMC5217681.
19) J. Jiang, Y. Wang, L. Susak, H. Chan, R. Basu, Z. H. Zhou, and J. Feigon, "Structure of telomerase with telomeric DNA", *Cell* **173**, 1179-1190 (2018). https://doi.org/10.1016/j.cell.2018.04.038. PMCID in process.

D. Research Support

NIH R01 GM48123 (Feigon) 09/01/15-08/31/19 Role: PI
Structure and Function of Human Telomerase
The main goals of this proposal are to determine the molecular basis of telomerase catalytic activity, by determining the structure and investigating the dynamics and function of the catalytic core of Tetrahymena and vertebrate telomerase.

NIH R01 GM107567 (Feigon) 09/01/14-08/31/18 Role: PI
Structure and assembly of regulatory RNPs
The aims of this proposal are to investigate the structure and assembly of the 7SK RNP. Specifically, we will determine how the stable RNP core proteins hLARP7 and MePCE interact with the 7SK RNA.

NSF MCB-1022379 (Feigon) 09/01/15-08/31/20 Role: PI
Structure and function of Tetrahymena telomerase accessory proteins
This aims of this proposal are to investigate the structure, dynamics, interactions, and function of *Tetrahymena* telomerase holoenzyme accessory proteins p19, p45, p75, and p50 using NMR, X-ray crystallography, cryo-electron microscopy, and biochemical methods.

Completed support: not applicable

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: Yao He

eRA COMMONS USER NAME (credential, e.g., agency login): YAOHE2

POSITION TITLE: Postdoctoral Fellow at UCLA

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
University of Science & Technology of China (USTC), Hefei, P. R. China	B.S.	09/2007	06/2011	Biology
USTC, Hefei, P. R. China	Ph.D.	09/2011	06/2017	Biochemical and Molecular Biology
University of California-Los Angeles Los Angeles, California	Postdoctoral	10/2017	Current	Biochemistry Biophysics

A. Personal Statement

My academic training and research experience to data have provided me with excellent background in biochemistry and molecular biology. My graduate thesis focused on revealing the ion selectivity mechanism of potassium channels (NaK and NaK2K channels) in native-like membrane environment by structural and electrophysiological analysis under my mentor Dr. Changlin Tian. I have experience in expression and purification of membrane proteins along with characterization of these proteins in different kinds of membrane environment (detergent micelle, lipid bilayer and nanodisc). After optimizing the protocol for proteoliposome reconstruction, I was able to obtain high quality solid-states NMR spectra and process those data for structural and dynamic analysis (Shi et al., *Nature Communications* 2018). Another project during my graduate period was the folding and structural study of chemical synthesized toxin polypeptides. I was able to refold these disulfide bond rich polypeptides in physiological buffer conditions and determine their structures by using solution NMR methods (Cui et al., *Angew Chem Int Ed Engl* 2013; Pan et al., *Chem Commun* 2014). I was always inspired by newly solved structures since they could provide such a lot detailed structural information and help me verifying my hypothesis.

After finishing my graduate studies, I decided to broaden my knowledge of structure biology by moving into the field of cryoEM. I have chosen Dr. Z. Hong Zhou and Dr. Juli Feigon as my postdoctoral advisors to study the structure and function of Telomerase ribonucleoprotein (RNP) complex. Telomerase complex plays fundamentally important role in maintaining genome integrity during replication and its dysfunction in human is related to cancer development. I am currently optimizing the protocol for Telomerase cryoEM sample preparation by adding different kinds of DNA primers into the sample and I hope we could obtain an atomic resolution structure of this complex to give us a better understanding of Telomerase assembling and translocation.

For the past year, I was trained in cryoEM sample preparation, data collection, structure refinement and model building. My previous knowledge of biochemistry and ongoing experiences of cryoEM is suited to assist in the accomplishment of this project. Additionally, I would be able to further my understanding of protein-RNA interaction by studying the genome packing, transcription and regulation in double-stranded RNA viruses under the guidance of Dr. Z. Hong Zhou. Overall, I am excited to participate in this proposed project.

B. Positions and Honors

Positions and Employment

10/2017-Current Postdoctoral Fellow, Department of Microbiology, Immunology and Molecular Genetics (MIMG) and Department of Medicine at the David Geffen School of Medicine University of California-Los Angeles, Los Angeles, California

09/2011-06/2017 Graduate Researcher, School of Life Sciences, University of Science and Technology of China, Hefei, Anhui, China

Honors

2012 National Scholarship of China
2016 National Scholarship of China

C. Contributions to Science

1. **Ion selectivity and dynamic study of potassium channels:** NaK channel is a non-selective cation channel that can conduct both sodium and potassium with equally high efficiency. Mutations in the selectivity filter region could transform NaK channel into a potassium selective channel (termed as NaK2K channel). These features make NaK and NaK2K channels unique models to investigate the selectivity mechanism of potassium channels. During my graduate research, I have purified these channels with detergent and reconstructed them into lipid bilayers to study their ion selectivity and dynamics in native-like membrane environment by using single-channel recording and solid-state NMR methods. Based on the observations, we proposed that structural plasticity within the selectivity filter and the selection of these conformations by different ions were key molecular determinants for highly efficient conduction of different ions in non-selective cation channels. Below, I have listed the publication that is related to this project.
   a. Shi C*, **He Y***, Hendriks K*, de Groot BL, Cai X, Tian C, Lange A, Sun H. A single NaK channel conformation is not enough for non-selective conduction. *Nature Communications.* 2018; 9(1):717. doi:10.1038/s41467-018-03179-y. PMCID: PMC5818664.

2. **Structure determination of chemical synthesized toxin polypeptides:** Animal toxins are known to target a wide variety of receptors and ion channels with high affinity and specificity, and they are important pharmacological tools for studying ion channel structure-function relationships, gating mechanisms and tissue localization. But the inability to isolate sufficient quantities of pure toxin from animal has been a major bottleneck to structural and functional studies. In this project, my collaborator developed several new strategies to synthesis these disulfide bond rich toxin polypeptides (e.g. toxin Mambalgin-1, 57 amino acids and 4 disulfide bonds). I focused on the refolding of these peptides in physiological buffer conditions, tested their function with biochemical or electrophysiological experiments, and determined their structure by using solution NMR methods. Below, I have listed publications related to this project.
   a. Cui HK*, Guo Y*, **He Y***, Wang FL, Chang HN, Wang YJ, Wu FM, Tian CL, Liu L. Diaminodiacid-based solid-phase synthesis of peptide disulfide bond mimics. *Angew Chem Int Ed Engl*. 2013; 52(36):9558. doi: 10.1002/anie.201302197. PMCID:
   b. Pan M*, **He Y***, Wen M, Wu F, Sun D, Li S, Zhang L, Li Y, Tian C. One-pot hydrazide-based native chemical ligation for efficient chemical synthesis and structure determination of toxin Mambalgin-1. *Chem Commun (Camb)*. 2014; 50(44):5837. doi: 10.1039/c4cc00779d.

c. Zheng JS*, **He Y***, Zuo C, Cai XY, Tang S, Wang ZA, Zhang LH, Tian CL, Liu L. Robust chemical synthesis of membrane proteins through a general method of removable backbone modification. J Am Chem Soc. 2016; 138(10):3553. doi: 10.1021/jacs.6b00515.

* Co-first authorship

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1JEcg4hHCXcsEy/bibliography/55266070/public/?sort=date&direction=ascending.

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

Completed Research Support