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Biological Neutron Scattering: A Collaboration with the Oak Ridge Center for Structural Molecular Biology

Principal Investigator, Jill Trewhella, University of Utah

SUMMARY

The overarching goal of this project was to promote applications of small-angle scattering in structural molecular biology by providing model examples of cutting edge applications that demonstrate the unique capabilities and potential of the DOE national user facilities at Oak Ridge, especially the newly commissioned BioSANS. The approach taken was three-fold: (1) to engage in high impact collaborative research projects that would benefit from small-angle neutron scattering to both demonstrate the power of the technique while expanding the potential user community; (2) to provide access to scattering facilities established at the University of Utah to as broad a set of researchers as possible to increase the expertise in small-angle scattering generally; and (3) to develop new methods and tools for small-angle scattering.

To these ends, three major research collaborations were pursued that resulted in a significant body of published work where neutron scattering and contrast variation played a major role. These major collaborations involved studies of protein complexes involved in (1) bacterial transcription regulation and adaptive response (a DOE/BER priority area); (2) regulation of cardiac muscle; and (3) neuronal disorders. In addition, to broaden the impact of the project, smaller collaborative efforts were supported that used either small-angle X-ray or neutron scattering. Finally, the DOE supported facilities at the University of Utah were made available to researchers on a service basis and a number of independent groups took advantage of this opportunity.

In all of this work, there was an emphasis on the training of students and post docs in scattering techniques, and a set of publications (a book chapter, a review, and an encyclopedia article) were produced to guide the non-specialist potential user of scattering techniques in successful applications of the techniques. We also developed a suite of user friendly web-based computational tools currently being accessed world-wide by researchers as an aid in neutron scattering data interpretation.

In all, these collaborative projects and resulted in 29 original refereed journal articles published between 2005 and 2010 and engaged groups from at least 14 Universities (10 US, 4 international) and 3 National Laboratories (2 US, 1 international).

An important final initiative from this project was to begin a process for international community agreement on a set of standards for the publication of biomolecular small-angle scattering data. This initiative is being championed with the International Union of Crystallography and has engaged a number of Journal Editors and is a very important step in the maturing of this now burgeoning field.

RESULTS FROM COLLABORATIVE RESEARCH APPLICATIONS OF X-RAY AND NEUTRON SCATTERING

1. Protein Complexes in Bacterial Transcription Regulation and Adaptive Response.

The Sporulation Histidine Kinase KinA and its Inhibitor, with Mitchell Guss, David Langley, David Jacques, University of Sydney, William Burkholder, Stanford, Glenn King, U. Queensland, Tracy Hanley, ANSTO, Boualem Hammouda, NIST

This project began with small-angle X-ray and neutron contrast variation studies [**9,14**] of two distinctive protein inhibitors (Sda and KipI) of the sensor histidine kinase KinA that is responsible for the initiation of spore formation in *Bacillus subtilis*. Interest in KinA signaling and inhibition lies in the fact that sensor histidine kinases provide the principal means by which bacteria sense environmental signals and trigger the needed adaptive response (at the level of gene transcriptional regulation) for survival; e.g. movement toward nutrients, pathogenesis, sporulation. Histidine kinases are not found in mammals, and so their inhibitors provide a potential means for modulating bacterial adaptive responses; for example in combating infection without negative side effects in the host. Our studies to date reveal important similarities and differences between Sda and KipI inhibition of KinA; both inhibitors bind to the helical bundle that is the dimerization histidine-phosphotransfer domain, but KipI shows a much larger binding interface that includes the conserved proline. The structural data suggest that KipI binding is via its C-terminal cyclophilin-like domain that may induce a *cis-trans* peptidyl isomerization in this proline that would result in an inhibitory signal being transmitted via the 4-helix bundle formed by the KinA dimerization domains. Our KinA-Sda studies also suggest that the dimerization domain of KinA is used as a signal transduction conduit for the inhibition, but in this case the conserved proline and residues in its vicinity are not involved. These differences may confer the distinct specificity on the KinA-KipI interaction that is not observed for KinA-Sda. Together these studies provide a growing body of evidence on how environmental signals that affect bacterial adaptive responses might be modulated, ultimately to manage bacterial populations; e.g. defeating pathogenesis or for biotechnology applications.

The KipI inhibitor of KinA is in turn regulated by a binding partner known as KipA and KipI-KipA homologues are present throughout a diverse number of totally unrelated bacterial species; from bacteria that inhabit sea ice to those that have adapted to hot springs, deep sea hydrothermal vents and even squid ink. A genomic analysis of several bacterial species reveals that in 80 % of cases where a KipI homologue gene is present the KipA homologue gene also exists. Despite the apparently strong evolutionary relationship between KipI and KipA there remains sufficient sequence divergence amongst KipI and KipA homologues to suggest that the proteins adopt different functions. Of the hundreds of known KipI and KipA homologues a few have been categorized as regulators of bacterial sporulation whilst others have been categorised as enzymes, including urea carboxylase, allophanate hydrolase, biotin-dependent carboxylase and even an exoribonuclease. Of all the putative functions of the KipI-KipA proteins, however, only one has been experimentally investigated - the role of KipI and KipA in the control of *B. subtilis* sporulation.

Using neutron contrast variation we developed the first structural model of a KipI-KipA complex [**22**], and in the process solved the crystal structure of the first KipI-KipA homologue; from *Thermus thermophilus* (native diffraction data to 2.1 Å). The structure from the thermophile reveals four domains; 2 KipI domains and 2 KipA domains. Both KipA domains are structural

homologues of the cycolphilin-like *B. subtilis* KipI-C domain we previously solved by crystallography. With these crystal structures, and an NMR structure of the KipI-N domain we also solved, we were able to develop a detailed structural model of the *B. subtilis* KipI-KipA complex by refining the domain positions and orientations against our neutron contrast variation data. The structure reveals a novel 'bicyclophilin cleft' that is highly conserved and thus appears to be the active site for this novel and widely utilized bacterial protein.

With these studies, for which neutron contrast variation has been a central tool, we are building toward a description of multiple protein pathways in this model bacterial signal transduction pathway that links bacterial responses to the environment.

The Bacterial Transcription Regulator LacI, with Liskin Swint-Kruse, Hongli Zhan, University of Kansas Medical Center

In a series of small-angle X-ray scattering studies of the bacterial transcription regulator Lactose repressor protein (LacI), we examined the role of conformational changes and structural flexibility in DNA binding and allosteric signaling.

We showed that removal of operator DNA from LacI results in an unfolding and extension of the hinge-helix that connects the LacI regulatory and DNA-binding domains, and that the LacI inducer IPTG that modulates operator DNA affinity results only in very small adjustments in the orientations of domains and/or sub-domains within the structure. Notably, the crystal structure of the native LacI-operator DNA complex differs significantly from its average solution conformation. The solution scattering data are best-fit by an ensemble of structures that includes (1) ~60% of the V-shaped dimer-of-homodimers observed in the crystal structure, and (2) ~40% of molecules with more "open" forms, such as those generated when the homodimers move with respect to each other about the tetramerization domain. In gene regulation, such a flexible LacI would be beneficial for the interaction of its two DNA binding domains, positioned at the tips of the V, with the requirement for binding two of three LacI operators for full repression. These results are published in [**17**]**.**

Further scattering and thermodynamic studies of an engineered chimeric bacterial transcription regulator were designed to allow us to probe the role of the sequence that links the DNA-binding and regulatory domains on DNA binding and allosteric signaling. We found that although DNA-binding site residues are identical in the chimera and LacI, the chimera failed to discriminate between alternative DNA ligands as well as LacI, indicating that long-range functional contributions must be propagated across the interface between the DNA binding and regulatory domains. We also found that the chimera has less conformational flexibility than LacI, which correlates with the increased promiscuity in DNA-binding. Finally, chimera variants with single amino acid changes in the linker sequence show a range of functional effects. These results are published in [**15**].

2. Protein Complexes Regulating Cardiac Muscle, with Paul R. Rosevear, U. Cincinnati and Samantha P. Harris, University of California, Davis

The multi-subunit muscle complex troponin, responsible for the regulation of myosin cross-bridge formation between the thick and thin filaments of muscle that drives the contractile cycle, has been a major target for structural studies for some years. Crystal structures of both the skeletal and cardiac isoforms were published in relatively recent times, although the cardiac isoform in particular has large missing regions, likely due to flexible and mobile regions. Our

paper reporting the solution structure for the bisphosphorylated form of the cardiac N-extension of troponin I ($cTnI_{1-32}$), a region for which there were no previous high resolution data, is now in print [10]. Our model for the troponin complex, based on this structure combined with crystal structure data, suggests a molecular mechanism for the observed changes in myosin cross-bridge kinetics upon TnI phosphorylation, and a structural framework for understanding cardiac myopathies that are due to impairment of the Ca^{2+}-troponin-mediated regulatory signals.

More recently we have turned our attention to cardiac myosin binding protein-C (cMyBP-C), another accessory protein of striated muscle that is vital for maintaining regular heart function. Its four N-terminal regulatory domains, C0-C1-m-C2 (C0C2), influence actin and myosin interactions, the basic muscle contractile proteins. Using neutron contrast variation, we have determined that C0C2 forms a repeating assembly with filamentous actin [**13**], where the C0- and C1-domains of C0C2 attach near the DNase-I binding loop and sub-domain 1 of adjacent actin monomers. Direct interactions between the N-terminus of cMyBP-C and actin thereby provide a mechanism to modulate the contractile cycle by affecting the regulatory state of the thin filament and its ability to interact with myosin.

3. Protein Complexes Implicated in Neuronal Disorders, with Palmer Taylor, Davide Comoletti, University of California, San Diego

This project has focused on the neuroligins; postsynaptic cell adhesion molecules capable of triggering synapse formation and maturation upon binding to presynaptic α and β-neurexins. Genomic data indicate that this family of proteins is linked to autism and mental retardation, disorders that are devastating in terms of prevalence, family impact, and cost to society. Using a combination small-angle scattering with neutron contrast variation, sequence analysis, modeling, biochemical and mutagenesis data we put forward a model of the α-neurexin and β-neuroligin complex in the synaptic space [**8,18**]. Our more recent solution structural studies on the highly elongated, multidomain α-neurexin has revealed that is has distinctive functional properties compared to β-neurexin [**23**]. Electron microscopy shows α-neurexin has an overall "Y" shape, with two mayor points of flexibility. Using rigid body modeling against small angle X-ray scattering data we confirms that the protein maintains this characteristic Y shape in solution. These results help us to understand how α-neurexin-1 fits in the synaptic cleft and associates with multiple ligands. A manuscript reporting these results is in preparation.

4. Additional Collaborations Utilizing DOE Supported Small-Angle Scattering Facilities

We have collaborated with a number of new research groups using small-angle X-ray and neutron scattering to study proteins and protein complexes (specifically studies combining NMR and small-angle scattering Data for improved bio-molecular solution structure determination with Alex Grishaev and Ad Bax at the NIH [**1,11**]; of protein kinase A studies with Susan Taylor, UC San Diego [**2,3**]; of biomateirals with Bruce Yu at the University of Utah and then University of Maryland [**4,26**]; of protein folding and molecular crowding with David Goldenberg at the University of Utah [**16,27**]; of the Tom70 mitochondrial import receptor oligomer with Terry Mulhern at University of Melbourne [**21**], of the picornaviral loop-to-loop replication protein-RNA complex with Stephen Pascal at the University of Massey [**20**], of the pyruvate kinase enzyme for investigations of the requirements for allosteric inhibition with Aron Fenton and University of Kansas Medical Center [**25**], of the HIV-1 MA protein complexed with the host protein calmodulin with Wes Sundquist and Chris Hill at the University of Utah [**24**].

We provided access to scattering facilities to researchers for small-angle scattering, including in preparation for future neutron scattering studies [**33,34,35**]. The new groups include investigators at the University of Utah, University of Maryland, Case Western Reserve, and University of Texas Medical Branch (Galveston) who are or will be publishing work that acknowledges this award for providing scattering facilities.

METHODOLOGY DEVELOPMENT AND OUTREACH

1. Tools for Planning and Analyzing Neutron Contrast Variation Experiments

Small-angle neutron contrast variation data provides structural parameters to guide the construction of molecular models for model refinements. These parameters also provide a quality check on your data and a measure of its real information content. We implemented some useful analysis methods along these lines with a user-friendly web-based interface (MULCh: ModULes for the analysis of small-angle neutron contrast variation data from biological complexes) [**12**]. This web site is being accessed by neutron users worldwide.

We published one book chapter with another in press [**29,31**], an encyclopedia article [**30**], a review [**31**] and journal articles [**5,6,7**] demonstrating the power of neutron scattering in studying protein structure and to guide different kinds of users (*e.g.* graduate students, molecular biologists not trained in physical techniques) in how to successfully use small-angle neutron scattering to study biomolecular structures and reliably interpret results. We also regularly taught the neutron scattering modules in the European Molecular Biology Organization (EMBO) Practical Course on Solution Scattering form Biological Macromolecules (http://www.embl-hamburg.de/biosaxs/courses.html)

2. Standards for Publication of Biomolecular Small-Angle Scattering, with Dmitri Svergun, EMBL, Hamburg and the International Union of Crystallography (IUCr) Small-Angle Scattering Commission.

In a paper published in 2009 [**19**], we describe how modeling scattering data from a small protein that formed oligomers in solution was misinterpreted due to insufficient accuracy in protein concentration determinations. In 2008, at the invitation of the editor of the Proceedings of the National Academy of Science, a commentary was written on the disputed interpretation of small-angle scattering data from highly concentrated proteins solutions [**27**]. In this commentary it was noted that in the context of the now burgeoning field of small-angle scattering applications in biology the need for standards for the publication of small-angle scattering data, especially for structural results in the protein field, without which the broader nonexpert community is bound to treat the results of these studies with at best caution and at worst skepticism if we continue to see work published that does not meet the standards required for reliable interpretation. We began a conversation on this topic of publication standards at the 2008 meeting of the International Union of Crystallography in Osaka, initially engaging the IUCr Commissions for Small-Angle Scattering, Biological Macromolecules and Journals. This conversation has further developed and a draft paper describing a set of standards has been drfafted (by Trewhella, Jacques, Guss, and Svergun) and is being circulated among the members of the Small-Angle Scattering Commission for recommendation to the IUCr.

REFEREED JOURNAL PUBLICATIONS RESULTING FROM THE PROJECT AND REFERENCED IN THE REPORT

2005

1. Grishaev, A., Wu, J., Trewhella, J., and Bax, A. "Refinement of Multi-Domain Structures by Combination of Solution Small-Angle X-ray Scattering and NMR Data," *J. Am. Chem. Soc. 127*, 16621- 16628, 2005.
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4. Ramachandran, S., Trewhella, J., Tseng, Y., and Yu, Y. B. "Coassembling Peptide-Based Biomaterials: Effect of Pairing Equal and Unequal Chain Length Oligopeptides," *Chemistry of Materials 18*, 6157-6162, 2006
5. Trewhella, J. "Structural Themes and Variations in Protein Kinase A as seen by Small-Angle Scattering and Neutron Contrast Variation," *Eur. Biophys. J. 35*, 585-589, 2006.
6. Trewhella J. "Protein Kinase A Targeting and Activation as Seen by Small-angle Solution Scattering," *Eur. J. Cell Biol. 85*, 655-662, 2006.
7. Trewhella, J. "Neutrons Reveal How Nature Uses Structural Themes and Variation in Biological Regulation," *Physica B 385-86*, 825-830, 2006.

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8. Comoletti, D., Grishaev, A., Whitten, A.H., Tsigelny, I., Taylor, P. and Trewhella, J. "Synaptic Arrangement of the Neuroligin/β-Neurexin Complex Revealed by X-Ray and Neutron Scattering," *Structure 15*, 693-705, 2007
9. Whitten, A. E., Jacques, D. A., Hamouda, B., Hanley, T., King, G. F., Guss, M. J., Trewhella, J. and Langley, D. B., The Structure of the Sda-KinA Complex Suggests an Allosteric Mechanism of Histidine Kinase Inhibition," *J. Mol. Biol. 368*, 407-420, 2007
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13. Whitten, A. E, Jeffries, C. M., Harris, S. P., and Trewhella J. "Cardiac myosin binding protein-C decorates F-actin: Implications for cardiac function," *Proc. Natl. Acad. Sci USA 105*, 18360-18365, 2008
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17. Taraban, M., Zhan, H., Whitten, A. E., Langley, D. B., Matthews, K., Swint-Kruse, L., and Trewhella, J. "Ligand-induced Conformational Changes and Conformational Dynamics in the Solution Structure of the Lactose Repressor Protein," *J. Mol. Biol*. *376*, 466-481, 2008.
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25. Fenton, A. W., Williams, R. and Trewhella, J. "Changes in Small-Angle X-ray Scattering Parameters Observed upon Binding of Ligand to Rabbit Muscle Pyruvate Kinase Are Not Correlated with Allosteric Transitions," *Biochemistry 49*, 7202-7209, 2010.
26. Ramachandran, S., Taraban, M. B., Trewhella, J., Gryczynski, I., Gryczynski, Z and Yu, Y. B. "Effect of Temperature During Assembly on the Structure and Mechanical Properties of Peptide-Based Materials," *Biomacromolecules 11*, 1502-1506, 2010.

Book Chapters, Reviews, Pedogogical Articles, or Invited Commentary

27. Trewhella, J. The Different Views from Small Angles. Invited commentary *Proc. Natl. Acad. Sci USA 105*, 4967-4968, 2008
28. Whitten, A. E. and **Trewhella, J.** "Small-Angle Scattering and Neutron Contrast Variation for Studying Bio-molecular Complexes," Microfluids, Nanotechnologies, and Physical

Chemistry (Science) in Separation, Detection, and Analysis of Biomolecules, Methods in Molecular Biology Series, James W. Lee Ed., Human Press, USA, Volume 544, pp307-23, 2009.

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Publications from users of the DOE SAXS facilities at the University of Utah that acknowledge this award

32. Tsalkova, T, Blumenthal, D. K., Mei, F.C., White, M.A., and Cheng, X **"**Mechanism of Epac Activation: Structural and Functional Analyses of EPAC2 Hinge Mutants with Constitutive and Reduced Activities," *J. Biol. Chem. 284*, 23644-23651, 2009.
33. Johnson, T., Gupta, K., Albright, T, and Kiser, P. "Segmented Polyurethane Intravaginal Rings for the Sustained Combined Delivery of Antiretroviral Agents Dapivirine and Tenofovir," *The European Journal of Pharmaceutical Sciences 39*, 203-212, 2010.
34. Jamros, M. A., Oliveira, L. C., Whitford, P. C ., Onuchic, J. N., Adams, J. A., Blumenthal, D.K., Jennings, P. A. "Proteins at work: a combined small angle X-RAY scattering and theoretical determination of the multiple structures involved on the protein kinase functional landscape," *J Biol Chem. 285*, 36121-36128, 2010

INVITED TALKS

2005

Neutrons Reveal How Nature Uses Structural Themes and Variations in Biological Regulation. Neutrons in Biology, a satellite meeting of the International Union for Pure and Applied Biophysics Congress/EBSA Biophysics Congress, Grenoble France, Sept 4-7, 2005 and International Conference on Neutron Scattering, Sydney, Australia, Nov 27-Dec. 2 2005

Structural Themes and Variations in PKA Targeting and Activation. 1st International Meeting on Anchored cAMP Signaling Pathways, Berlin Germany, Oct. 15-16, 2005

Small-angle Scattering for Structure Determination of Macromolecules. Emerging Science Initiative for Synchrotron Science: Symposium and Workshop, Melbourne, Australia, April 12-13, 2005

Tackling Molecular Machines: The Structures Underlying Muscle Contraction. 30th Annual Lorne Conference on Protein Structure and Function, Phillip Island, Australia, Feb 6-10, 2005

2006

Small-Angle Scattering with a Focus on Biomolecular Structure. American Crystallographic Association 2006 Annual Meeting, Honolulu, Hawaii, July 22-27, 2006.

Scattering of Neutrons, Basics. EMBO Practical Course on Solution Scattering from Biological Macromolecules, Hamburg, October 23-30, 2006

Neutron Contrast Variation and Understanding the Bio-Molecules that Regulate Bacterial Sporulation. 5th AINSE/ANBUG Neutron Scattering Symposium, Lucas Heights, December 11-13, 2006 and Australian Biophysical Society Meeting, Sydney, December 11-13, 2006

2007

Biomolecular Signaling and Regulation; A solution Scattering View. Asian Crystallographic Association, AsCA 2007, Taiwan, November 4-7, 2007; and Pittsburgh Diffraction Conference, Buffalo, NY, October 25-26, 2007

Neutrons and the Life Sciences. SNS/HFIR User's Meeting, Oak Ridge, TN, October 8-10, 2007

Small-angle X-ray Scattering and Neutron Contrast Variation Reveal the Arrangement of Synaptic Proteins Implicated in Autism. Crystal 25 Meeting of the Society for Crystallography in Australia and New Zealand, Hunter Valley, NSW, April 10-13, 2007; Neutrons in Biology, Satellite Meeting of the European Biophysics Congress, Oxfordshire, United Kingdom, July 11-13, 2007; and American Crystallographic Association Annual Meeting, Salt Lake City, Utah, July 21-26, 2007

Probing Biomolecular Complexes and Interactions with Neutrons. Future Directions in Physical Biosciences, University of Melbourne, May 14-15, 2007

Neutron Contrast Variation and Understanding Regulation of Bacterial Sporulation. Biomolecular Dynamics and Interactions: From single molecules to complex assemblies, University of Melbourne, February 2, 2007

2008

Keynote Lecture, Protein Structure Analysis Using Hybrid Data; NMR, Crystallography, and Small-Angle Scattering. The Australian and New Zealand Society for Magnetic Resonance 2008 Conference, South Stradbroke Island, December 7-11, 2008

Plenary Talk. Structural Studies of Biomolecular Signalling and Regulation using Combined Methods: Small-angle Scattering, Crystallography and NMR. Australian Society for Biophysics, 32nd Annual Meeting, Canberra, September 28-October 1, 2008

Keynote Lecture, Combined methods: Small-angle Scattering with NMR and Crystallography. XXI Congress of the International Union of Crystallography, Osaka, Japan, August 23-31, 2008

Transactions Talk, Combining High-Resolution Structures with Small-Angle Scattering and Neutron Contrast Variation Data for Studying of Protein Complexes in Solution. American Crystallographic Association Meeting, Knoxville TN, May 31-June 5, 2008

MiniSymposium Talk, Modeling Protein Complexes by Combining High-Resolution Structure with Small-Angle X-ray and Neutron Contrast Variation Data. Minisymposium on Structural Refinement and Modeling Guided by Low-Resolution Experimental Data at the 52nd Annual Meeting of the Biophysical Society and the 16th IUPAB International Congress, Long Beach CA, February 2-6, 2008

Scattering of Neutrons, Basics. EMBO Practical Course on Solution Scattering from Biological Macromolecules, Hamburg, October 19-26, 2008

2009

Plenary Talk: Protein Complexes in Biomolecular Signalling; The View from Small-Angles. XIV International Conference on Small-Angle Scattering; SAS2009, Oxford, UK, September 13-19, 2009

2010

Complementary use of SAXS and SANS. **EMBO Practical Course on Solution Scattering from Biological Macromolecules, Hamburg, October 25 - November 1, 2010**

Keynote Lecture: Protein Complexes in Biomolecular Signalling; The View from Small-Angles. 10th International Conference on Biology and Synchrotron Radiation, Melbourne, February 15-18, 2010

AWARDS

Jill Trewhella, Australian Federation Fellow, 2005

Jill Trewhella, Fellow, American Neutron Scattering Society, 2010