BIOGRAPHICAL SKETCH

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NAME: Peisley, Alys A.

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

POSITION TITLE:Research Investigator

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 Melbourne, Melbourne, Australia	BSc(Hons)	03/1999	Biochemistry and Molecular Biology
University of Melbourne, Melbourne, Australia	PhD	12/2006	Biochemistry and Molecular Biology
Stanford University, Palo Alto, CA	Postdoc	10/2008	Immunology/Structural Biology
Harvard University, Boston, MA	Postdoc	05/2014	Immunology/Structural Biology
University of Michigan, Ann Arbor, MI	Postdoc	05/2017	Structural Biology

A. Personal Statement

I have a long term interest in understanding the structural basis of mechanisms coupling conformational change to signal propagation in large protein complexes.. With a diverse background in structural biology methodology that includes training in NMR spectroscopy, x-ray crystallography and single particle electron microscopy I bring an integrative approach to understanding the structural basis of biochemical mechanisms. I have expertise in protein expression and purification and biochemical characterization and have successfully applied my knowledge to the purification of difficult and challenging proteins and protein complexes. Previously I have pioneered the use of biochemical, x-ray crystallographic and single particle electron microscopy methodology to discover and understand the dynamic filamentous signaling mechanisms of the viral ds-RNA pattern recognition receptors RIG-I and MDA5. Coupled to recent advances in the structural biology of membrane proteins I now seek to extend my repertoire to the structural characterization of signaling complexes of the melanocortin receptor system.

B. Positions and Honors

2003-2005 Research Associate, CSIRO Molecular Health Technologies, Parkville, Australia.
2017-present Research Investigator, University of Michigan, Ann Arbor, MI.

Honors and Awards

2009-2010 GSK Alliance Fellowship, Immune Disease Institute, Boston, MA.
2007-2008 Dean’s Postdoctoral Fellowship, Stanford University, Palo Alto, CA.
1999-2002 Australian Postgraduate Award, Commonwealth Government of Australia.

C. Contributions to Science

My early work in structural biology involved the high resolution x-ray crystal structure determination of barley exoglucohydrolase, HvExoI, bound to substrate analogs by molecular replacement. HvExoI releases a single glucose moiety from non-reducing termini of oligo- and polymeric β-d-glucosides to support seed germination and plant development. The observation of differing catalytic sub-site occupancies by various analogs relative to an entrapped glucose molecule that remains bound at the end of the catalytic cycle suggested a processive mechanism for hydrolysis of a polymeric substrate. An extensive collaborative research effort and intensive multi-scale molecular modeling resulted in the description of a novel conveyer belt-like substrate-assisted processive catalytic mechanism.

a. Streltsov VA, Luang S, Peisley A, Varghese JN, Ketudat Cairns JR, Fort S, Hijnen M, Tvaroška I, Ardá A, Jiménez-Barbero J, Alfonso-Prieto M, Rovira C, Mendoza F, Tiessler-Sala L, Sánchez-Aparicio JE, Rodríguez-Guerra J, Lluch JM, Maréchal JD, Masgrau L, Hrmova M. Discovery of processive catalysis by an exo-hydrolase with a pocket-shaped active site. Nature Communications. 2019; 10(1):2222.

My prior post-doctoral work involved the mechanistic understanding of the discrimination of viral dsRNA by the innate immune pattern recognition receptors RIG-I and MDA5. We were the first to observe the dynamic filamentous assembly of MDA5 and RIG-I as a shared mode of viral dsRNA recognition, where kinetic filament assembly proceeds upon recognition of a specificity determinant, MDA5 according to length and RIG-I according to unmodified 5'triphosphate dsRNA ends. The mechanism of length dependent recognition of viral dsRNA by MDA5 was determined through measurements of ligand binding affinity, binding kinetics and enzyme activity and through the visualization of complex assembly by electron microscopy. Proximity induced oligomerization of CARD domains within the filament assembly as a common mechanism for signal induction through the signaling adaptor MAVS was also demonstrated. This work also laid the foundation for in group collaboration to determine a crystal structure of MDA5 bound to dsRNA and for the role of RIG-I and MDA5 in overcoming viral evasion mechanisms.

a. Alys Peisley, Cecilie Lin, Bin Wu, McGhee Orme-Johnson, Liu, M, Thomas Walz and Sun Hur, Cooperative assembly and dynamic disassembly of MDA5 filaments for viral dsRNA recognition, Proceedings of the National Academy of Sciences, 2011, 108(52):21010-5.

b. Qian Feng, Stanleyson V. Hato, Martijn A. Langereis, Jan Zoll, Richard Virgen-Slane, Alys Peisley, Sun Hur, Bert L. Semler, Ronald van Rij, Frank J.M van Kuppeveld, MDA5 detects the double-stranded RNA replicative form in picornavirus-infected cells, Cell Reports, 2012, 2(5):1187-96.

c. Alys Peisley, Myung Hyun Jo, Cecilie Lin, Bin Wu, McGhee Orme-Johnson, Thomas Walz and Sun Hur, Kinetic Mechanism for Viral dsRNA Length Discrimination by MDA5 Filaments, Proceedings of the National Academy of Sciences, 2012, 109(49):E3340-9.

d. Alys Peisley, Bin Wu, Hui Yao, Thomas Walz and Sun Hur, RIG-I forms signaling-competent filaments in an ATP-dependent and ubiquitin-independent manner, Molecular Cell, 2013, 51(5):573-83.

e. Bin Wu, Alys Peisley, Hui Yao, Claire Richards, Thomas Walz and Sun Hur, Structural Basis of Viral dsRNA Recognition by MDA5, Cell. 2013, 152(1-2):276-89.

f. Yao H, Dittmann M, Peisley A, Hoffmann HH, Gilmore RH, Schmidt T, Schmid-Burgk JL, Hornung V, Rice CM, Hur S. ATP-dependent effector-like functions of RIG-I-like receptors. Molecular Cell, 2015; 58(3):541-8.

The mechanism of viral dsRNA recognition was further extended to structural understanding of the role of CARD domain oligomerization within the filamentous assembly for CARD-CARD domain communication and

induction of filament assembly of the signaling adaptor protein MAVS. K_{63}-linked ubiquitin chains had been shown to regulate RIG-I signaling through CARD domains. We found that non-covalently attached K_{63}-linked ubiquitin was sufficient to induce tetramer formation of the RIG-I CARD domains and were able to crystallize this complex. Determination of the structure revealed a helical assembly of the CARD domains stabilized by ubiquitin chains and provided the first evidence of helical nucleation as a mechanism for signal transduction by the RLRs. This work also laid the foundation for a collaborative effort resulting in the crystallization of the RIG-I 2CARD:Ub:MAVS CARD complex and of the MAVS filament cryo-EM reconstruction.

a. Alys Peisley, Bin Wu, Hui Xu, Z. James Chen and Sun Hur, Structural basis for ubiquitin-mediated antiviral signal activation by RIG-I, Nature, 2014, 509(7498):110-4.

b. Bin Wu, Alys Peisley , David Tetrault, Zongli Li, Edward H. Egelman, Katharine E. Magor, Thomas Walz, Pawel A. Penczek and Sun Hur, Molecular Imprinting as a Signal-Activation Mechanism of the Viral RNA Sensor RIG-I, Molecular Cell. 2014; 55(4):511-23.

In the transition to structural studies membrane protein complexes I have published methods on the use of electron microscopy for analysis of GPCR complexes.

a. Peisley A , Skiniotis G. 2D Projection Analysis of GPCR Complexes by Negative Stain Electron Microscopy. Methods in Molecular Biology, Springer Protocols. 2015;1335:29-38.

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

Bibliography

1. Streltsov VA, Luang S, Peisley A , Varghese JN, Ketudat Cairns JR, Fort S, Hijnen M, Tvaroš ka I, Ardá A, Jiménez-Barbero J, Alfonso-Prieto M, Rovira C, Mendoza F, Tiessler-Sala L, Sánchez-Aparicio JE, Rodríguez-Guerra J, Lluch JM, Maréchal JD, Masgrau L, Hrmova M. Discovery of processive catalysis by an exo-hydrolase with a pocket-shaped active site. Nature Communications. 2019; 10(1):2222.

2. Peisley A , Skiniotis G. 2D Projection Analysis of GPCR Complexes by Negative Stain Electron Microscopy. Methods in Molecular Biology, Springer Protocols. 2015;1335:29-38.

3. Yao H, Dittmann M, Peisley A, Hoffmann HH, Gilmore RH, Schmidt T, Schmid-Burgk JL, Hornung V, Rice CM, Hur S. ATP-dependent effector-like functions of RIG-I-like receptors. Molecular Cell, 2015; 58(3):541-8: Editorial choice: Foley, J.F., "Viral sensors get more involved" May 19 2015, Science Signaling 8(377): pp. ec130.

4. Bin Wu, Alys Peisley , David Tetrault, Zongli Li, Edward H. Egelman, Katharine E. Magor, Thomas Walz, Pawel A. Penczek and Sun Hur, Molecular Imprinting as a Signal-Activation Mechanism of the Viral RNA Sensor RIG-I, Molecular Cell. 2014; 55(4):511-23. Commentary: Hopfner KP. RIG-I holds the CARDs in a game of self versus nonself. Molecular Cell. 2014; 55(4):505-7.

5. Alys Peisley , Bin Wu, Hui Xu, Z. James Chen and Sun Hur, Structural basis for ubiquitin-mediated antiviral signal activation by RIG-I, Nature, 2014, 509(7498):110-4. Commentary: Zhu S, Jackson R, Flavell RA. The lock-washer: a reconciliation of the RIG-I activation models. Cell Res. 2014; 24(6): 645-6.

6. Alys Peisley , Bin Wu, Hui Yao, Thomas Walz and Sun Hur, RIG-I forms signaling-competent filaments in an ATP-dependent and ubiquitin-independent manner, Molecular Cell, 2013, 51(5): 573-83. Highlighted in Faculty1000Prime

7. Bin Wu, Alys Peisley , Hui Yao, Claire Richards, Thomas Walz and Sun Hur, Structural Basis of Viral dsRNA Recognition by MDA5, Cell. 2013, 152(1-2):276-89. Research Highlight: Yvonne Bordon. Making and breaking MDA5 filaments, Nature Reviews Immunology 13, 153 (March 2013)

8. Alys Peisley & Sun Hur, Cellular Recognition of viral dsRNA, Review, Cellular and Molecular Life Sciences. 2013, 70(11):1949-63.

9. Qian Feng, Stanleyson V. Hato, Martijn A. Langereis, Jan Zoll, Richard Virgen-Slane, Alys Peisley , Sun Hur, Bert L. Semler, Ronald van Rij, Frank J.M van Kuppeveld, MDA5 detects the double stranded RNA replicative form in picornavirus-infected cells, Cell Reports, 2012, 2(5):1187-96.

10. Alys Peisley, Myung Hyun Jo, Cecilie Lin, Bin Wu, McGhee Orme-Johnson, Thomas Walz and Sun Hur, Kinetic Mechanism for Viral dsRNA Length Discrimination by MDA5 Filaments, Proceedings of the National Academy of Sciences, 2012, 109(49):E3340-9.

11. Alys Peisley, Cecilie Lin, Bin Wu, McGhee Orme-Johnson, Liu, M, Thomas Walz and Sun Hur, Cooperative assembly and dynamic disassembly of MDA5 filaments for viral dsRNA recognition, Proceedings of the National Academy of Sciences, 2011, 108(52):21010-5.

12. Wu, H, Peisley, A, Graef IA, Crabtree, GR., NFAT signaling and the invention of vertebrates, Trends in Cell Biology. 2007, 17(6):251-60.

13. Peisley A. A., Gooley P. R., High-level expression of a soluble and functional fibronectin type II domain from MMP-2 in the Escherichia coli cytoplasm for solution NMR studies, Protein Expression and Purification, 2007, 53(1):124-31.