BIOGRAPHICAL SKETCH
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NAME: Hill, Christopher Peter

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

POSITION TITLE: Distinguished Professor of Biochemistry

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 York, Heslington, England	B.A.	06/1980	Chemistry
University of York, Heslington, England	D.Phil.	06/1987	Chemistry
University of York, Heslington, England	Postdoctoral	05/1988	Chemistry
University of California, Los Angeles	Postdoctoral	06/1992	Structural Biology

A. PERSONAL STATEMENT

We take structural approaches, coupled with biochemistry, genetics, and cell biology, to understanding a variety of biological processes. Historically, our primary structural approach has been X-ray crystallography, although at this time most of our structural studies use cryo-EM. Our first cryo-EM structures have been determined in collaboration with Peter Shen, who remains a partner in our ongoing studies. Collaboration with the NYSBC has been important for our published work on the AAA ATPase Vps4 (eLife, 2017). Continued collaboration with the NYSBC has been critical for recent subsequent studies on Vps4 that have provided considerable new insight to substrate processing, and are about to be submitted for publication with Venkata Dandey (NYSBC) as a co-author. Those most recent studies used spotiton to good effect to achieve improved integrity of the Vps4-Vta complex, presumably by "outrunning" collisions with the air interface. The current proposal is related to the earlier Vps4 studies, and seeks to determine the structure of functional p97 complexes. Preliminary data indicate a serious orientation bias that we hope can be overcome using spotiton. Successful outcome will provide important mechanistic insight to a critical cellular machine that is an established therapeutic drug target, and will likely complement the earlier collaborative findings by advancing a unified mechanistic model of AAA ATPase function.

Hill-lab publications of cryo-EM structures:

Monroe N, Han H, Shen PS, Sundquist WI, **Hill CP**. (2017). Structural basis of protein translocation by the Vps4-Vta1 AAA ATPase. *Elife* 6. pii: e24487.

Han H, Monroe N, Sundquist WI, Shen PS, **Hill CP**. (2017). The AAA ATPase Vps4 binds ESCRT-III substrates through a repeating array of dipeptide-binding pockets, *Elife. Nov 22:6*. pii e31324. Doi: 10.7554/eLife.31324.

Han H, Fulcher J, Dandey VP, Sundquist WI, Kay MS, Shen PS, **Hill CP**. (In preparation). Implications for AAA+ ATPase processing of protein substrate loops from the structure of Vps4 bound to a circular peptide

B. POSITIONS AND HONORS

Positions and Employment

1992-1998 Assistant Professor, Department of Biochemistry, University of Utah
1998-2000 Associate Professor, Department of Biochemistry, University of Utah

2000-2009	Professor, Department of Biochemistry, University of Utah
2009-Present	Distinguished Professor, Department of Biochemistry, University of Utah
2009-Present	Department Co-Chair, Department of Biochemistry, University of Utah

Other Experience and Professional Memberships

2000, 2009	ASBMB National Meeting Theme Organizer
2001-2003	Director, Interdepartmental Graduate Program in Molecular Biology
2001-2009	SSRL proposal review committee and NIH Advisory Board
2006-2009	SSRL Scientific Advisory Committee
2006-2009	Member, School of Medicine Appointment, Retention, Promotion and Tenure Committee
2007	Co-Chair, Gordon Research Conference on Proteins.
2007	Local chair, American Crystallographic Association Annual Meeting.
2007, 2011	Session chair, American Crystallographic Association Annual Meeting
7-9,12,14-16	Chair, NIH study sections
2008-2012	Chartered Member, NIH study section on Membrane Biology and Protein Processing
2011-now	Chair, U of Utah SOM Basic Science Working group
2013-18	Editorial board. Journal of Biological Chemistry
2014-now	Chair, NE-CAT (APS synchrotron) Scientific Advisory Board
2014-15	Editor, Current Opinion in Structural Biology: Macromolecular Machines and Assemblies
2017	Chair, West Coast Protein Crystallography Workshop
2018-now	Member, OSHU Cryo-EM Advisory Board

Honors and Awards

1994-1997	American Cancer Society Junior Faculty Research Award
2004	Eccles Visiting Scholar, Southern Utah University
2006	Prahl Award for best PhD thesis in the U Utah Health Sciences (Andreas Forster)
2008	Prahl Award for best PhD thesis in the U Utah Health Sciences (Robert Fisher)
2010-2014	Leo T. and Barbara K Samuels Presidential Chair
2013	Protein Society. Dorothy Crowfoot Hodgkin Award.
2014-	H.A. and Edna Benning Presidential Chair

C. CONTRIBUTIONS TO SCIENCE

1. ESCRT pathway/HIV budding/innate immunity/inhibition of virus entry

   Our contributions to the understanding of HIV have included insights to the mechanism of ESCRT pathways in viral budding and to inhibitory process of innate immunity and novel therapeutic lead compounds. These include the structural/biochemical basis for interactions with ubiquitin, which are important for substrate recruitment and/or assembly of the budding machinery. In a series of six manuscripts, we determined the mechanisms by which the ESCRT adaptor protein ALIX recruits substrate and binds the ESCRT-III complex that drives budding. We also made fundamental discoveries on VPS4, the ATPase that drives budding, including the cryo-EM structure of an active complex that explains the mechanism of protein translocation by a broad family of AAA ATPases, including the proteasome, NSF, and p97. Our contributions to understanding of innate immunity have included the structural characterization of BST2/tetherin, which prevents virions from escaping from the host cell and subsequently targets them for internalization and degradation. Our contribution to the development of novel D-peptide inhibitors, which have potential against HIV and many other viral and cellular targets, are collaborative with Michael Kay. These have included structures of multiple complexes (many to be published) that explain the basis for binding, explain mechanisms of resistance, and guide the development of improved inhibition properties.

   a) Fisher RD, Chung HY, Zhai Q, Robinson H, Sundquist WI, **Hill CP**. (2007). Structural and biochemical studies of ALIX/AIP1 and its role in retrovirus budding. *Cell*, *128*(5), 841-52.

   b) Bajorek M, Schubert HL, McCullough J, Langelier C, Eckert DM, Stubblefield WM, Uter NT, Myszka DG, **Hill CP**, Sundquist WI. (2009). Structural basis for ESCRT-III protein autoinhibition. *Nat Struct Mol Biol*, *16*(7), 754-62. PMCID: PMC2712734

   c) Monroe N, Han H, Shen PS, Sundquist WI, **Hill CP**. (2017). Structural basis of protein translocation by the Vps4-Vta1 AAA ATPase. *Elife* 6. pii: e24487. PMCID: in progress

d) Han H, Monroe N, Sundquist WI, Shen PS, **Hill CP**. (2017). The AAA ATPase Vps4 binds ESCRT-III substrates through a repeating array of dipeptide-binding pockets, *Elife. Nov 22:6*. pii e31324. Doi: 10.7554/eLife.31324. PMCID: in progress

2. HIV Architecture

We determined multiple structures of the primary structural components of the HIV virion. These include the HIV MA protein, which revealed an unexpected trimeric assembly and positively charged membrane-binding surface. Our structures of the HIV CA NTD in complex with CypA revealed details of this functionally important interaction and explained the basis for CypA prolyl cis-trans isomerase activity. Our structures of multiple HIV CA CTD constructs revealed the basis for its dimerization, and our associated biochemical analysis and collaborative biological studies explained its importance in virus assembly. In collaborative studies, we determined the first EM structures of HIV CA tubes, which revealed the hexameric assembly that underlies the architecture of the HIV (and other retroviral) capsid. We subsequently determined the first structures of an HIV CA hexamer, and also determined the structural basis for binding of a novel class of assembly inhibitors that show promise as therapeutic lead compounds. Together, this work provided a foundation upon which much of the current understanding of HIV virion architecture has been built.

a) Gamble TR, Vajdos FF, Yoo S, Worthylake DK, Houseweart M, Sundquist WI, **Hill CP**. (1996). Crystal structure of human cyclophilin A bound to the amino-terminal domain of HIV-1 capsid. *Cell*, *87*(7), 1285-94.

b) Gamble TR, Yoo S, Vajdos FF, von Schwedler UK, Worthylake DK, Wang H, McCutcheon JP, Sundquist WI, **Hill CP**. (1997). Structure of the carboxyl-terminal dimerization domain of the HIV-1 capsid protein. *Science, 278*(5339), 849-53.

c) Howard BR, Vajdos FF, Li S, Sundquist WI, **Hill CP**. (2003). Structural insights into the catalytic mechanism of cyclophilin A. *Nat Struct Biol*, *10*(6), 475-81.

d) Pornillos O, Ganser-Pornillos BK, Kelly BN, Hua Y, Whitby FG, Stout CD, Sundquist WI, **Hill CP**, Yeager M. (2009). X-ray structures of the hexameric building block of the HIV capsid. *Cell*, *137*(7), 1282-92. PMCID: PMC2840706

3. Nucleosome remodeling and reorganizing complexes

The FACT and Spt6 histone chaperones are essential in yeast, and function in a variety of roles that include disassembly and reassembly of nucleosomes in coordination with DNA replication and gene expression. Although they are unrelated to each other, we have shown that they both bind to all of the histone components of the canonical nucleosome. We have reported crystal structures of most of the domains of both FACT and Spt6, and in each case have completed biochemical characterization that includes identification and quantification of interactions with relevant binding partners. This includes determining the structural basis and mechanistic consequence of FACT's interaction with histones H2A-H2B. We are also pursuing a parallel investigation of the SWI-SNF/RSC chromatin remodelers, which slide nucleosomes to regulate multiple processes, including gene expression. Successes in this area include determining the foundational structure of a remodeler Arp subcomplex and discovering a remarkable mechanism that appears to regulate the timing of association with chromatin.

a) McDonald SM, Close D, Xin H, Formosa T, **Hill CP**. (2010). Structure and biological importance of the Spn1-Spt6 interaction, and its regulatory role in nucleosome binding. *Molecular Cell*, *40*(5), 725-35. PMCID: PMC3017428

b) Schubert HL, Wittmeyer J, Kasten MM, Hinata K, Rawling DC, Heroux A, Cairns BR, **Hill CP**. (2013). Structure of an actin-related subcomplex of the SWI/SNF chromatin remodeler. *Proc Natl Acad Sci U S A*, 110(9), 3345-50. PMCID: PMC3587198

c) Kemble DJ, McCullough LL, Whitby FG, Formosa T, **Hill CP**. (2015) FACT disrupts nucleosome structure by binding H2A-H2B with conserved peptide motifs. *Molecular Cell*, 60(2):294-306. PMCID: PMC4620744

d) Sdano MA, Fulcher JM, Palani S, Chandrasekharan MB, Parnell TJ, Whitby FG, Formosa T, **Hill CP.** (2017) A novel SH2 recognition mechanism recruits Spt6 to the doubly phosphorylated RNA polymerase II linker at sites of transcription. *Elife*, August 17, published on-line. PMCID: in progress

4. Proteasome Activation, UCH deubiquitylase mechanism and regulation, protein quality control

The proteasome performs the bulk of proteolysis in the cytosol and nucleus to drive multiple cellular pathways. Our structural and biochemical studies of proteasome-activator complexes (11S, Blm10, and the Pba1/2 assembly factor) that revealed the principles of binding and gate opening. We also characterized the subunit RPN13 and UCH37, which associate with each other and, because of flexibility, cannot be visualized in the current EM reconstructions. Unpublished recent work, reveals mechanisms of RPN13 recruitment and suggests a regulatory pathway that might allow development of novel therapeutics. Studies of Vms1 are providing insights to how this quality control factor acts upstream of the proteasome.

a) Whitby FG, Masters EI, Kramer L, Knowlton JR, Yao Y, Wang CC, **Hill CP**. (2000). Structural basis for the activation of 20S proteasomes by 11S regulators. *Nature*, *408*(6808), 115-20.

b) Sadre-Bazzaz K, Whitby FG, Robinson H, Formosa T, **Hill CP**. (2010). Structure of a Blm10 complex reveals common mechanisms for proteasome binding and gate opening. *Molecular Cell*, *37*(5), 728-35. PMCID: PMC2859072

c) VanderLinden RT, Hemmis CW, Schmitt B, Ndoja A, Whitby FG, Robinson H, Cohen RE, Yao T, **Hill CP**. (2015) Structural basis for the activation of the UCH37 deubiquitylase. *Molecular Cell* 57(5):901-11. PMID:25702872. PMCID: PMC4355076

d) Neilson JR, Fredrickson EK, Waller TC, Rendón OZ, Schubert HL, Lin Z, **Hill CP**, Rutter J. (2017). Sterol Oxidation Mediates Stress-Responsive Vms1 Translocation to Mitochondria. *Molecular Cell*. 68(4):673-685. PMCID: in progress

5. Heme biosynthesis and tetrapyrrole metabolism

This program advanced structural and biochemical understanding of proteins that function in tetrapyrrole metabolism, including heme biosynthesis. Highlights included determining the catalytic mechanism of URO-D, coproporphyrinogen oxidase, uroporphyrinogen III synthase, biliverdin IXalpha reductase, PrmC/HemK, SirC, Gun4, and Met8 proteins.

a) Mathews MA, Schubert HL, Whitby FG, Alexander KJ, Schadick K, Bergonia HA, Phillips JD, **Hill CP**. (2001). Crystal structure of human uroporphyrinogen III synthase. *EMBO J*, *20*(21), 5832-9. PMCID: PMC125291

b) Schubert HL, Raux E, Brindley AA, Leech HK, Wilson KS, **Hill CP**, Warren MJ. (2002). The structure of Saccharomyces cerevisiae Met8p, a bifunctional dehydrogenase and ferrochelatase. *EMBO J*, *21*(9), 2068-75. PMCID: PMC125995

c) Phillips JD, Whitby FG, Kushner JP, **Hill CP**. (2003). Structural basis for tetrapyrrole coordination by uroporphyrinogen decarboxylase. *EMBO J*, *22*(23), 6225-33. PMCID: PMC291847

d) Phillips JD, Warby CA, Whitby FG, Kushner JP, **Hill CP**. (2009). Substrate shuttling between active sites of uroporphyrinogen decarboxylase is not required to generate coproporphyrinogen. *J Mol Biol*, *389*(2), 306-14. PMCID: PMC2705282

Complete List of 121 PubMed-listed Publications in MyBibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/christopher.hill.1/bibliography/40518952/public/?sort=date&direction=descending

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D. RESEARCH SUPPORT

Ongoing Research Support

R01GM112080 (Sundquist) 07/01/14 - 06/30/18 (NCE)
NIH/NIGMS
ESCRT-III and MIT Protein Complexes in Cytokinesis
The three aims of the current funding cycle were to perform: 1) biochemical analyses of ESCRT-III filament formation, 2) biochemical and structural analyses of MIM-MIT interactions, and 3) functional analyses of ESCRT-III complexes in abscission. This is the grant that is under consideration for competitive renewal.
Role: Co-Investigator

R01GM112129 (Rutter/Hill MPI) 07/01/15 – 06/30/19

NIH/NIGMS
An Interdisciplinary Approach to Stress-Induced Mitochondrial Quality Control
Structure and biochemistry of Vms1 localization, mechanism and regulation of Vms1 mitochondrial translocation, and biochemical and physiological role of Vms1 in mitochondrial maintenance.
Role: Co-PI

R01GM116560 (Hill/Formosa MPI) 05/01/16 – 04/30/20
NIH/NIGMS
Structure, Mechanism, and Function of the Histone Chaperones Spt6 and FACT
Molecular processes regulating nucleosome structure and transcription.
Role: Co-PI

5P50GM082545-11 (Sundquist) 08/01/07 – 07/31/22
NIH/NIGMS
Center for the Structural Biology of Cellular Host Elements in Egress, Trafficking, and Assembly of HIV (CHEETAH Center)
Role: Co-Investigator

HIV Release and Restriction Proj 1
Determine the structural bases for membrane remodeling by ESCRT-III filaments and VPS4, characterize how mammalian retroCHMP3 (ESCRT-III) proteins inhibit HIV budding without inducing cellular toxicity, and image ESCRT assemblies within budding virions by electron cryotomography.

Future Dir: Latency & Immune Receptors Proj 5
Use hu-mice to determine the pathway of viral reactivation from latency at the anatomical and cellular levels, determine molecular mechanisms that are important for the establishment, maintenance, and reversal of latency, and decipher molecular mechanisms that mediate immune responses.

Biological Reagents Core 1
Provide peptide, protein, antibody, and RNA reagents. Membrane proteins will be produced. Peptide synthesis will produce ligands, inhibitors, and protein fragments. Larger peptides/proteins, including with site-specific labels, will be produced using native chemical ligation. An automated high-throughput phage display screening and characterization platform will produce Fab antibody fragments for use as crystallography chaperones, cryo-EM fiducials, biochemistry/cell biology tools, and to stabilize/trap heterogeneous protein complexes in specific conformations for structural studies.

Structural Biology Core 2
Provide capabilities for visualizing structures of macromolecules, subcellular complexes, cells and tissues. X-ray crystallography is used to determine multiple high-resolution structures. Electron crystallography will provide structures from 2D crystals, e.g., HIV-1 CA, the Gag:CTD-SP1, and TRIM5α.

Biology Core 5
Provide technical support and generate advanced biological reagents to support mechanistic and structural studies of HIV-1 replication and transmission

R01GM127783 (Chandrasekharan) 04/01/18 – 03/31/23
NIH/NIGMS
Structure, function and regulation of the H2B ubiquitin-conjugating complex
Determine structure /mechanism of the H2B ubiquitin-conjugating complex and of phosphorylated Rad6.
Role: Collaborator

Completed Research Support

R21 CA191929 (Hill) 12/01/12 – 11/30/16
NIH/NCI
Establish RPN13-proteasome association as a novel anticancer target
Establish an alternative approach to inhibiting aspects of proteasome function.
Role: PI