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: Carolyn M. Teschke

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

POSITION TITLE: Professor and Associate Department Head

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 Wisconsin-Eau Claire	BS	05/83	Chemistry
Washington State University	PhD	09/90	Biochemistry
Massachusetts Institute of Technology	Post-doc	08/94	Biochemistry/Biophysics

A. Personal Statement

The goal of my lab's work is to investigate how weak protein interactions support the high-fidelity assembly of an icosahedral virus. Specifically, we are determining how different domains in bacteriophage P22's coat protein are involved on the determination of size and morphology of the capsid. We are also working to understand how scaffolding protein, the protein catalyst for the assembly reaction, is involved in nucleation and elongation of procapsids. Scaffolding protein is also involved in the incorporation of the portal protein complex at a unique vertex in the capsid. We are working to understand the mechanisms by which all these proteins interact to achieve the proper assembly product. I have worked with P22 since I was a post-doc, so I have the extensive experience in the field. In addition, I have worked on protein folding, and protein interactions since I was a graduate student. For instance, we characterized the chaperone-independent folding of P22 coat protein, and how GroEL/S interacts and assists in the folding of variant coat proteins. My laboratory established that procapsid assembly is a reversible reaction. This discovery was significant because it allowed the first application of rigorous, thermodynamic analysis to a two-protein assembly system, when coat and scaffolding protein assemble into virus-like procapsid particles. Implementation of rigorous thermodynamic analysis led to generalizable knowledge about virus assembly. For example, we found that the individual subunit interactions of a procapsid are weak but because of the additive nature of the interactions, the association energy of procapsids is very large. We have established methods that allow us to screen for interesting mutants and through these we have found coat variants that assemble into particles with different morphologies, including helical arrays and petite heads. My lab played a major role in a collaborative effort to solve two pseudoatomic resolution models of coat protein, which were a real boon to our research. Recently we completed a solution NMR structure of an inserted domain in P22 coat protein and determined it is crucial for folding and stability of coat protein. We are now investigating the structure and function of I-domains in P22-like phages that have only 15-25% sequence identity to P22's coat protein. We are actively pursuing the process by which capsid nucleation occurs through a detailed understanding of the interactions of coat, scaffolding and portal proteins, and RNA. I have assembled an excellent team of collaborators, including cryoEM and NMR experts, with whom I have worked for many years.

Ongoing projects that I would like to highlight include:

R01GM076661
Teschke (PI)
09/23/2019 – 06/30/2023
Understanding the Protein: Protein Interactions Required for Virus Assembly

R21AI156838
Simon White (PI), Teschke (coI), Michael Lynes (coI)
12/1/2020 – 11/30/2022
Characterization of long-circulating phages isolated from in vivo mouse studies

R01AI149727
Miraim Braunstein (PI), Teschke (PI) subcontract
01/03/2020 – 12/31/2021
A Novel Protein Export Chaperone of Mycobacterium Tuberculosis

B. Positions, Scientific Appointments, and Honors

Positions and Employment

1983-1990 Doctoral Graduate Student, Washington State University; Advisor: Dr. Linda L. Randall
1991-1994 Post-doctoral Associate, MIT; Advisor: Dr. Jonathan A. King
1994-2000 Assistant Professor, Dept. of Molecular and Cell Biology, University of Connecticut.
2000-2008 Associate Professor, Dept. of Molecular and Cell Biology, University of Connecticut
2008-present Professor, Depts. of Molecular and Cell Biology, and Chemistry, University of Connecticut
2016-present Associate Department Head for MCB, University of Connecticut

Additional Professional Education

HERS Bryn Mawr Summer Institute for Women in Higher Education Administration, Summer 2013
COACh training for career building workshops, Summer 2016

Honors

Stage 2 Editorial Board reviewer for the NIH Director's New Innovator Award, 2022
Fulbright U.S. Scholar, University of York, 1/2022-5/2022
AAAS Council Delegate, Section on Biological Sciences, elected, 2020-2023
Editorial Board, Journal of Virology, 2020-2023
Associate Editor, Science Advances, AAAS, 2018-
Committee on the Status of Women in Microbiology, American Society of Microbiology, 2018-2024
Alice C. Evans Award, American Society of Microbiology, 2018
Basic Science Awards Nominating Committee, American Society of Microbiology, 2016-2019
Jefferson Science Fellow, serving at the U.S. State Dept., 2015-16
Embassy Science Fellow, 2016
Fellow of the AAAS, elected, 2015
Co-organizer for FASEB summer conference on Virus Structure and Assembly, 2014
Co-vice organizer for FASEB summer conference on Virus Structure and Assembly, 2012
Co-organizer for the New England Structure Symposium, 2006, 2017
Nominating committee for the Protein Society, elected, 2005-2009
Connecticut Academy of Arts and Sciences, elected member

Other Experience and Professional Memberships

NSF ad hoc reviewer, 2017, 2019, 2020
NIH Ad Hoc reviewer Prokaryotic Molecular and Cell Biology study section, 2008, 2009, 2010, 2016
Ad hoc reviewer for NIH F31 fellowship in Molecular Genetics, 2007
University of Kansas Cobre grants, 2007, 2016
Ad hoc Grant Reviewer for United States-Israel Binational Science Foundation,1998, 2004, 2006
Member: ASM, ASV, ASBMB, AAAS

C. Contribution to Science

We investigate the ability of viral proteins to assemble into complexes Specifically, we study the assembly of viruses using bacteriophage P22 as a model. Our goal is to understand how viruses assemble, which will allow the design of inhibitors of the assembly process. My lab has also studied chaperoned protein Below I describe in broad strokes five major projects my lab has worked on and the significant contributions arising from each:

1. Viral capsid assembly—investigations of capsids:

Assembly of a virus is a highly coordinated process involving sequential addition of multiple proteins, ultimately leading to an infectious virion. How do weak interactions between individual proteins support assembly of a whole virus? Our work addresses how viruses assemble precisely into the proper size and shape, given their capsid proteins are pliable by design. We use bacteriophage P22 as a model dsDNA virus. In bacteriophage P22, herpesviruses, adenoviruses, and many other dsDNA viruses, the initial product of assembly is a precursor capsid (the protein shell of a virus) known as the procapsid, which undergoes a coordinated series of interactions to become the final mature capsid.

Assembly of phage P22 is a particularly tractable model where we can apply phage genetics with rigorous biochemical, biophysical and structural analyses of the reaction and assembly products. For instance in collaboration with Martin Jarrold's lab, we have determined the mass of entire phages. My lab played a major role in a collaborative effort to solve two near atomic resolution models of coat protein. In addition, my laboratory established procapsid assembly is a reversible reaction. This discovery was significant because it allowed the first application of rigorous, thermodynamic analysis to a complex assembly system. We found that the individual coat protein subunit interactions in a procapsid are weak but because of the additive nature of the interactions, the association energy of procapsids is very large.

1. Keifer, D.Z., Motwani, T., Teschke, C.M., Jarrold, M.F. (2016) Measurement of the accurate mass of a 50 MDa infectious virus. *Rapid Commun. Mass Spectrom.*, 30:1957-62. doi: 10.1002/rcm.7673.
2. Parent, K.N., Khayat, R., Tu, L.H., Suhanovsky, M.M., Cortines, J.R., Teschke, C.M., Johnson, J.E., Baker, T.S. (2010) P22 coat protein structures reveal a novel mechanism for capsid maturation: stability without auxiliary proteins or chemical crosslinks. *Structure*, 18, 390-401.
3. Parent, K.N., Suhanovsky, M.M., Teschke, C.M. (2007) Phage P22 procapsids equilibrate with free coat protein subunits. *J. Mol. Biol.*, 365, 513-22.
4. Parent K.N., Zlotnick, A., Teschke, C.M. (2006) Quantitative analysis of multi-component spherical virus assembly: Scaffolding protein contributes to the global stability of phage P22 procapsids. *J. Mol. Biol.*, 359,1097-106.

2. Viral capsid assembly—studies of scaffolding protein:

A scaffolding protein directs assembly of coat protein to form procapsids. We found a simple interaction between coat and scaffolding protein drives the proper assembly of the complex procapsids. Thus, in recent years my group has discovered that the protein:protein interactions required to generate a capsid should be disrupted readily, suggesting capsid assembly is a good drug target. We have recently developed a novel method to use NMR to investigate disorder inside a procapsid.

1. Cortines, J.R., Motwani, T., Vyas, A.A., Teschke, C.M. (2014) Highly specific salt bridges govern bacteriophage P22 icosahedral capsid assembly: identification of the site in coat protein responsible for interaction with scaffolding protein. *J. Virol.,* 88, 5287-97.
2. Padilla-Meier, G.P., Teschke, C.M. (2011) Conformational changes in bacteriophage P22 scaffolding protein induced by interaction with coat protein, *J. Mol. Biol.,* 410, 226-40.
3. Cortines, J.R., Weigele P.R., Gilcrease, E.B., Casjens, S.R., Teschke, C.M. (2011) Decoding bacteriophage P22 assembly: Identification of two charged residues in scaffolding protein responsible for coat protein interaction. *Virology*, 421, 1-11.
4. Whitehead III, R.D., Teschke, C.M.*, Alexandrescu, A.T.* (2019) NMR Mapping of Disordered Segments from a Viral Scaffolding Protein Encapsulated in a 23 MDa Procapsid Complex, bioXriv, [preprint]; doi: 10.1101/539965, *submitted to Biophys. J.*

3. Viral capsid assembly—studies of portal protein

Portal proteins of dsDNA phages and viruses are essential for both DNA packaging and ejection into host cells. As such, portal proteins are excellent targets for anti-viral compounds. When these viruses assemble, a portal protein complex is incorporated at only one vertex of the capsid. This specificity of assembly is not understood. We are characterizing the assembly of P22 procapsid with the portal ring. We have discovered that scaffolding protein catalyzes portal ring assembly and that portal nucleates assembly of procapids.

3. Motwani, T. Lokareddy, R.K., Dunbar, C.A., Cortines, J.R., Jarrold, M.F., Cingolani, G., Teschke, C.M. (2017) A viral scaffolding protein triggers portal ring oligomerization and incorporation during procapsid assembly. *Sci. Adv*. 3, e1700423. doi: 10.1126/sciadv.1700423. eCollection 2017 July.

4. Lokareddy, R., Sankhala, R., Roy, A., Afonine, P., Motwani, T., Teschke, C.M., Parent, K.N., and Cingolani, G. (2017) Portal protein functions akin to a DNA-sensor that couples genome-packaging to icosahedral capsid maturation. *Nature Communications,* 8:14310. doi: 10.1038/ncomms14310.
5. Motwani, T., Teschke, C.M. (2019). The architect of virus assembly: portal protein nucleates procapsid assembly in bacteriophage P22. *J. Virol.*, 93:e00187-19. doi: 0.1128/JVI.00187-19.

4. Phage P22 coat protein folding and assembly:

The cytoplasm of a cell is a crowded environment with DNA, RNA and proteins, all found at very high concentrations, which can lead to misfolding and misassembly of new polypeptide chains. In bacteria there are many molecular chaperones, including GroEL and GroES, to assist in the folding and assembly of substrate polypeptides. but how chaperones recognize substrates remains unclear. The folding of coat protein of phage P22 is a particularly appropriate model for understanding how GroEL/S interact with substrate polypeptides because single amino acid substitutions, which lead to a temperature-sensitive-folding phenotype (*tsf*), cause coat protein folding intermediates to become substrates for the chaperones. WT coat protein, in contrast, does not require GroEL/S for folding. By investigating the folding of the *tsf* coat proteins my laboratory defined some of the mechanisms that target proteins to be substrates for chaperones.

1. D'Lima, N.G., Teschke, C.M. (2015) A molecular staple: D-loops in the I-domain of bacteriophage P22 coat protein make important inter-capsomer contacts required for procapsid assembly. *Journal of Virology,* 89, 10569-79.
2. Parent, K.N., Teschke, C.M. (2007) GroEL/S substrate specificity based on substrate unfolding propensity. *Cell Stress and Chaperones*, 12, 20-32.
3. Doyle, S.M., Anderson, E., Zhu, D., Braswell, E.H., Teschke, C.M. (2003) Rapid unfolding of a domain populates an aggregation-prone intermediate that can be recognized by GroEL. *J. Mol. Biol.*, 332, 937-951.
4. Nakonechny, W.S., Teschke, C.M. (1998) GroEL and GroES control of substrate flux in the in vivo folding pathway of phage P22 coat protein. *J. Biol. Chem.*, 273, 27236-27244.

5. Folding and NMR studies of P22 coat protein I-domain:

Recently, we completed a solution NMR structure of an inserted domain in P22 coat protein and determined this small domain is crucial for folding and stability of the entire coat protein. The I-domain folds much faster than the remainder of the protein, and provides a folding nucleus for the unusal HK97 fold. We were the first group to ascribe a function for an accessory domain inserted into the HK97 fold.

1. Harprecht, C, Okifo, O, Robbins, K.J., Motwani, T., Alexandrescu, A.T., Teschke, C.M. (2016) Contextual Role of a Salt-Bridge in the Phage P22 Coat Protein I-Domain. *J Biol Chem.*; 291,11359-72. doi: 10.1074/jbc.M116.716910.
2. Newcomer, R., Fraser, L., Teschke, C.M., Alexandrescu, A.T. (2015) Mechanism of protein denaturation: partial unfolding of the P22 coat protein I-domain by urea binding, *Biophysical J.,* 109, 2666-77.
3. Rizzo, A.A., Suhanovsky, M.M., Baker, M.L., Fraser, L.C.R., Jones, L.M., Rempel, D.L., Gross, M.L., Chiu, W., Alexandrescu, A.A., Teschke, C.M (2014) Multiple functional roles of the accessory I-domain of bacteriophage P22 coat protein revealed by NMR structure and cryoEM imaging. *Structure,* 22, 830-41.
4. Suhanovsky, M.M. and Teschke, C.M. (2013) An intramolecular chaperone inserted in bacteriophage P22 coat protein mediates its chaperonin-independent folding, *J. Biol. Chem.,* 288, 33772-83.

Summary:

The research done in my lab has shown capsid assembly is a viable target for development of antiviral drugs because of the weak yet specific interactions required for the reaction. We have found regions of coat protein critical for assembly and discovered how simple interactions can control assembly. We have developed methods for the incorporation of the dodecameric portal complex into assembly procapsids, a first for phage P22. We have also investigated the mechanisms that proteins use to fold via interaction with cellular chaperones.

NCBI My bibliography URL

https://www.ncbi.nlm.nih.gov/sites/myncbi/1fA_Czh9bi2k7/bibliography/45934037/public/?sortby=pubDate&sdirection=descending

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

Active

Extramural:

NIH R01 GM076661 13-16 (PI, Teschke) 09/23/19 - 07/01/23
"Understanding the protein:protein interactions required for virus assembly

The long-term goal of our research is to achieve a mechanistic understanding of the protein:protein interactions involved in capsid assembly and define how those interactions are employed at each step to achieve an infectious virion, using bacteriophage P22 as a model dsDNA virus. The specific goals are to: 1) Define the mechanism of portal protein incorporation into procapsids; 2) Understand control of capsid morphology; 3) Understand how scaffolding protein functions in PC assembly.

R01 AI149727-01 (PI, Braunstein) 09/01/19 – 08/31/21
National Institute of Allergy and Infectious Diseases
"A Novel Protein Export Chaperone of Mycobacterium Tuberculosis"

The major goals of this project is to characterize the mechanism of SatS, a novel protein export chaperone of *Mycobacterium tuberculosis (Mtb)*. The Teschke lab will conduct biochemical and biophysical analysis of the chaperone-substrate (SatS-SapM) interaction to establish the basic principles of the system and determine the effect of this interaction on SapM folding.

Intramural:

UConn Research Excellence Program (PI, Alexandrescu; co-PI Teschke) 05/14/2018-06/30/2019
Structure and function of Phage L decorator protein

The goal of this project is to determine the structure of the phage L capsid decoration protein, and to determine how it binds to specific subsites the capsid. We will also investigate the role of Dec in interaction with capsids.

Completed Research Support

NIH R01 GM076661 years 10-13 (PI, Teschke) 09/01/16 - 03/01/19
"Understanding the protein:protein interactions required for virus assembly

The major goal of this project is to understand how viral capsids assemble with fidelity. The specific goals were to: 1) Define how communication between domains of coat protein affects capsid morphology; 2) Determine the structure and function of the I-domain from distantly related phages; 3) Elucidate the protein conformational changes occurring during assembly; 4) Investigate the assembly of the portal protein complex during PC assembly.

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: **Gino Cingolani, Ph.D.**

eRA COMMONS USER NAME (agency login): **cingolag**

POSITION TITLE: **Professor**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Bari, Italy	B.S./M.S.	07/1995	Biochemistry
University Joseph Fourier, Grenoble, France	D.E.A.	06/1996	X-ray Crystallography
European Molecular Biology Laboratory	Ph.D.	07/1999	Structural Biology
The Scripps Research Institute, CA, USA	Post-doc	12/2003	Virus Crystallography/Cell Biology

A. Personal Statement

My research interests and expertise lie in the field of Structural Biology. I trained in Biological Chemistry and Macromolecular Crystallography at different European Universities in the nineties. I moved to the United States in 1999 to continue my training at The Scripps Research Institute in the laboratories of Dr. Larry Gerace (Cell Biology) and Dr. Jack Johnson (Structural Virology). I have been a principal investigator since 2004, first at SUNY Upstate Medical University, and since 2009, at Thomas Jefferson University (TJU). For the last fifteen years, my laboratory has been continuously supported by multiple grants from NIH. Consistent with my multi-disciplinary training, my lab uses biophysical, biochemical, and cellular techniques to study macromolecules' structure and function. Our long-term goal is to employ rigorous chemical and physical methodologies to study medically-relevant problems that help decipher the most fundamental mechanisms of life and improve human health. Faithful to the idea that 'seeing is believing,' we investigate the structure of signaling and viral macromolecules as a starting point to probe their function and engineer their activity using small-molecule compounds. We are particularly interested in solving the atomic structures of 'druggable' biological targets linked to human diseases.

Currently, the main focus of my laboratory's research is to understand the molecular mechanisms of protein nuclear import and viral genome-delivery into gram-negative bacteria. Much of the work on nuclear import spearheaded from the pioneered structure of human importin β solved in complex with a classical (Cingolani et al, *Nature*, 1999) and non-classical (Cingolani et al., *Mol Cell*, 2002) import cargo, which I determined as a trainee. Over the last two decades, we have expanded the analysis of the structure/function of importins to importin α isoforms, with emphasis on the aberrant nuclear translocation of disease-associated transcription factors (STATS, NF-kB, RCC1, etc) and viral proteins. As far as the second research area, we study the mechanisms used by bacterial viruses to package genomes into empty capsid as well as eject genomes into Gram-negative. Both events occur through a dodecameric protein channel known as the portal protein (Olia et al., *NSMB* 2011; Lokareddy et al., *Nat Comms* 2017), which occupies a unique vertex of the icosahedral capsid breaking the icosahedral symmetry. We are particularly interested in bacteriophages used in phage therapy that eradicates human pathogens such as *Pseudomonas aeruginosa* and *Salmonella enterica*.

Throughout my career, I have maintained a strong commitment to graduate education. I have mentored eight Ph.D. students and four MS students, and I am currently mentoring four Ph.D. students in addition to four post-docs. I have developed and a graduate course (PR613) focused on biophysical methods in structural biology, and I teach a full graduate course in Biochemistry (PHRM 510) for Pharmacy students (a class of ~65 students). My service to the community includes serving as director of the X-ray Crystallography & Molecular Characterization Facility, one of the eight NCI-supported shared resources in the Sidney Kimmel Cancer Center at TJU. I also founded and developed the Jefferson Cryo-Electron Microscopy Core (JEMiCo), which is operational since March 2021 under my leadership. This state-of-the-art cryo-EM core boasts a new Glacios 200 kV cryo-transmission electron microscope equipped with a Falcon 4 direct electron detector, a Vitrobot, a glow discharger, and three multi-GPUs workstations for advanced cryo-EM image-processing. I also serve as Vice-Chair for Research of the Dept of Biochemistry and Mol Biology, and chair of the NIH Prokaryotic Cell and Molecular Biology (PCMB) study section panel. I have been the main PI on three shared instrumentation (S10) grants, all successfully funded, to acquire a hybrid diffractometer for macromolecular crystallography and bioSAXS, a crystallization robot, and associated equipment.

Cingolani, G., Petosa, C., Weis, K., and Mueller, C.W. (1999) Structure of importin β bound to the IBB domain of importin α. *Nature*, 399(6733): 221-229. PMID: 10353244.
Cingolani, G., Bednenko, J., Gillespie, M., and Gerace, L. (2002) Molecular basis for the recognition of a *non-classical* nuclear localization signal by importin β. *Molecular Cell*, 10: 1345-1353. PMID: 12504010.
Olia, A.S, Prevelige Jr., P.E., Johnson, J.E. and **Cingolani, G.** (2011) Three-dimensional structure of a viral genome-delivery portal vertex. *Nature Struc Mol Biol.* 18(5):597-603. PMCID: PMC3087855.
Lokareddy, R.K., Sankhala, R.S., Roy, A., Afonine, P.V., Motwani, T., Teschke, C.M., Parent, K.N. and **Cingolani, G.** (2017) Portal protein functions akin to a DNA-sensor that couples genome-packaging to icosahedral capsid maturation. *Nature Commun*. 8:14310. PMCID: PMC5290284.

Ongoing and recently completed projects that I would like to highlight include:

R35 GM140733
Cingolani (PI)
06/01/2021 – 05/31/2026
Mechanism of Viral Genome Delivery into Cells

R01GM122844
Cingolani (PI)
03/01/2018 – 12/31/2021
NIH/NIGMS
Regulation of Nuclear Import through Importin Alpha Isoforms

R01 AI137338
Niederweis, Cingolani (mPI)
04/01/2019 – 03/31/2024
Hemoglobin utilization by Mycobacterium tuberculosis

P01 NS097197
Minassian (PI), Role co-project lead
06/01/2016 – 05/31/2021 NCE
Genome Editing, mRNA suppression, and Glycogen Chain Termination to Inhibit Glycogen Storage as Therapy for Lafora Disease

P30 CA056036
Knudsen (PI), Role: director of the X-ray Crystallography Shared Resource
06/01/2018 – 5/31/2021
Translational Research in Cancer

R01 CA237398
Rodriguez-Bravo (PI), Role: co-investigator
12/01/2019 – 11/30/2024
Role of Nuclear Pore-Regulated Mechanisms in Prostate Cancer Aggressiveness

B. Positions and Honors

Positions

04/2017-present	Vice-Chair, Dept. of Biochemistry and Mol. Biology, Thomas Jefferson University, PA
06/2015-present	Director, X-ray Crystallography Facility, Sidney Kimmel Cancer Center
09/2015-12/2015	Visiting Professor, Dept. of Biochemistry and Mol. Biology, University of Bari, Italy
01/2015-present	Professor, Dept. of Biochemistry and Mol. Biology, Thomas Jefferson University, PA
06/2009-12/2014	Associate Professor with Tenure, Dept. of Biochemistry and Mol. Biology, Thomas Jefferson University, PA, USA
01/2004-05/2009	Assistant Professor, Dept. of Biochemistry and Mol. Biology, SUNY Upstate, NY, USA

Scientific Appointments

2021-2023	National Institute of Health (NIH) PCMB study section, chair
2018-2023	National Institute of Health (NIH) PCMB study section, permanent member
2018-present	European Union, Horizon 2020, reviewer
2017	National Institute of Health (NIH) ZRG1 F04B-D (20) L study section, reviewer
2016	National Institute of Health (NIH) ZRG1 F04B-D (20) L study section, reviewer
2015	Israel Science Foundation (ISF), ad hoc reviewer
2014	National Institute of Health (NIH) ZRG1 F04B-D (20) L study section, reviewer
2013	Italian Ministry of Health (MoH), Research Proposals, study section member
2013	National Institute of Health (NIH) ZRG1 F04-W(20) L study section, reviewer
2013	Advanced Photon Source (APS) beamlines NE-CAT's 24-ID-C and 24-ID-E, reviewer
2013	National Institute of Health (NIH) MFSC study section, ad hoc reviewer
2012	Italian Ministry of Health (MoH), Research Proposals, study section member
2012	National Institute of Health (NIH) ZRG1 F04-D (20) L study section, reviewer
2012	National Institute of Health (NIH) ZRG1 F04-K (09) L study section, reviewer
2012-present	Italian Scientists and Scholars in North America Foundation, member
2011	National Institute of Health (NIH) MFSC study section, ad hoc reviewer
2011	Research Grants Council (RGC) of Hong Kong, reviewer
2010	National Institute of Health (NIH) ZRG1 F04B-B(20) study section, reviewer
2010	National Institute of Health (NIH) ZGM1 CBB-0 (BC) U01 for Structural Biology, reviewer
2010	National Institute of Health (NIH) ZRG1 F05-C(20) L study section, reviewer
2009-2014	National Synchrotron Light Source (NSLS) Users' Committee beamline X6a, member
2008	National Science Foundation (NSF), ad hoc grant reviewer
2007-2009	American Society for Cell Biology (ASCB), member
2007-2008	Cornell High Energy Synchrotron Source (CHESS) Executive Committee, member
2007	National Science Foundation (NSF), panelist
2006-2007	Cornell High Energy Synchrotron Source (CHESS) Executive Committee, member
2006	Medical Research Council (MRC), UK, ad hoc grant reviewer
2004-2005	Cornell High Energy Synchrotron Source (CHESS) Express Mode proposal reviewer

Honors

2021	Vice-Chair, Jefferson Committee on Research (JCoR)
2019	Provost Award for Basic Research
2018	Fredric Rieders Faculty Prize in Graduate Education for Academic Year 2018-19
2017-present	Acta crystallographica D, co-Editor
2013	Jefferson Medical College Early Career Investigator Award
2004	Leukemia Research Foundation Young Investigator award
2000	Human Frontier Science Program (HFSP) post-doctoral fellowship
2000	Award for the best presentation at the TSRI Society of Fellows 4th symposium
1999	Award for the best presentation at the TSRI Society of Fellows 3rd symposium
1996	European Molecular Biology Laboratory (EMBL) pre-doctoral fellowship

C. Contribution to Science

1. The architecture of multisubunit ATPases involved in viral genome packaging. The main focus of my lab is to understand how double-stranded DNA viruses such as herpesviruses, adenoviruses, and tailed bacteriophages package their large genomes (~40-250 kb) inside empty precursor capsids (known as 'procapsids'). For over a decade, we have used the *Salmonella*-phage P22 as a model system for viral genome packaging. Using hybrid structural methods, we investigate the architecture, composition, and assembly of P22 packaging motor. We determined the portal protein changes conformation during genome-packaging and determined the structure of the mature (Olia et al., *NSMB*, 2011) and immature portal assembly (Lokareddy et al., *Nature Commun*, 2017). We also dissected the architecture of P22 small (TerS) and large (TerL) terminase subunit (Roy et al., *Structure,* 2012; Roy and Cingolani, *J Biol Chem*, 2012) and a complex of the two proteins (McNulty et al., *J Mol Biol*, 2015). Our current work focuses on the terminase subunits from Pseudomonas-phages that have direct applicability to phage therapy. We recently solved the structure of Pseudomonas PaP3

TerS, which led us to postulate a mechanism of sequence-specific DNA recognition by lateral interdigitation (Niazi et al., *submitted*). Key publications in this field include:

a. Olia, A.S, Prevelige Jr., P.E., Johnson, J.E. and **Cingolani, G.** (2011) Three-dimensional structure of a viral genome-delivery portal vertex. *Nature Struc Mol Biol.* 18(5):597-603. PMCID: PMC3087855.

b. Lokareddy, R.K., Sankhala, R.S., Roy, A., Afonine, P.V., Motwani, T., Teschke, C.M., Parent, K.N. and **Cingolani, G.** (2017) Portal protein functions akin to a DNA-sensor that couples genome-packaging to icosahedral capsid maturation. *Nature Commun*. 8:14310. PMCID: PMC5290284.

c. Niazi, M., Florio, T.J., Yang, R., Lokareddy, R.K., Swanson, N.A. Gillilan, R.E. and **Cingolani, G.** (2020) Biophysical analysis of Pseudomonas-phage PaP3 small terminase suggests a mechanism for sequence-specific DNA-binding by lateral interdigitation. *Nucleic Acid Res*. 48(20):11721-11736. PMCID: PMC7672466

d. Swanson, N.A., Lokareddy, R.K., Li, F., David, Hou C-F, Leptihn, S., Pavlenok, M., Niederweis, M., Pumroy, R.A., Moiseenkova-Bell, V.Y., **Cingolani, G.** (2021) Cryo-EM Structure of the Periplasmic Tunnel of T7 DNA-Ejectosome at 2.7 Å resolution. *Molecular Cell*. 81(15):3145-3159. PMCID: PMC8349896

2. Mechanisms and regulation of nucleocytoplasmic transport. Nucleocytoplasmic transport is central to the functioning of eukaryotic cells and is an integral part of the processes that lead to most human diseases. Nuclear availability of essential molecules such as transcription factors, DNA replication factors, and oncogenes is emerging as a powerful way to control gene expression, cellular differentiation, and transformation, as well as a novel and promising target *for pharmacological intervention.* In the first part of my carrier, I elucidated the molecular basis for recognition of *classical* (Cingolani et al., *Nature,* 1999) and *non-classical* (Cingolani et al., *Mol Cell,* 2002) import substrates by the transport factor importin β. As an independent investigator (2004-present), I studied the molecular basis for nuclear import of critical signaling molecules such as the phospholipid scramblase 1 (Chen et al., *J Biol Chem*, 2005) and 4 (Lott et al., *J Biol Chem*, 2010), the small nuclear ribonucleoprotein transporter snurportin (Mitrousis et al., *J Biol Chem*, 2008), the transcription factor STAT1 (Nardozzi et al., *J Mol Biol*, 2011) and the mechanisms of membrane protein translocation to the Inner Nuclear Membrane (Lokareddy et al., *structure*, 2015). More recently, my lab became interested in understanding the regulation of nuclear transport by importin α isoforms. We delineated the molecular basis for nuclear import of Influenza polymerase subunit Pb2 (Pumroy et al., *structure*, 2015) and RCC1 (Sankhala et al., *Nature Commun*, 2017) by the isoform importin α3. We recently determined the heterodimeric transcription factor NF-κB (p65:p50) is imported by the isoform importin α3 (Florio et al., *submitted*), and we are pursuing basic and translational studies on the ALS-related RNA-binding protein TDP-43. Overall, the long-term goal of our work is to decipher the mechanisms governing the nuclear entry of critical signaling molecules and to devise new small molecule inhibitors that could reduce aberrant nuclear translocation of signaling factors linked to cancer (Liao et al., *Mol Cancer Ther*, 2015; De Dominici et al., *Blood*, 2020). Key publications include:

a. **Cingolani, G.**, Petosa, C., Weis, K., and Mueller, C.W. (1999) Structure of importin β bound to the IBB domain of importin α. *Nature*, 399(6733): 221-229. PMID: 10353244.

b. **Cingolani, G.**, Bednenko, J., Gillespie, M., and Gerace, L. (2002) Molecular basis for the recognition of a *non-classical* nuclear localization signal by importin β. *Molecular Cell*, 10: 1345-1353. PMID: 12504010.

c. Pumroy, A.R., Ke, S., Hart, D.J., Zachariae, U. and **Cingolani, G.** (2015) Molecular determinants for nuclear import of Influenza A PB2 by importin α isoforms 3 and 7. *Structure.* 23(2): 374-384. PMCID: PMC4346194.

d. Sankhala, R.S., Lokareddy, R.K., Begum S., Pumroy, A.R., Gillilan, E.R. and **Cingolani, G.** (2017) Three-dimensional context rather than NLS amino acid sequence determines importin α subtype specificity for RCC1. *Nature Commun.* 8(1):979. PMCID: PMC5645467

3. Structure and inhibition of disease-related dual-specificity phosphatases. Dual specificity phosphatases (DSPs) are essential signaling enzymes whose misregulation is intimately linked to human diseases such as cancer, diabetes, inflammation, and Alzheimer's disease. The human genome encodes 38 DSPs (known as VH1-like phosphatases), which regulate critical aspects of the cell cycle. In my laboratory, we study the structure and function of disease-related DSPs. We have determined the atomic structure of the prototypical Vaccinia virus VH1 (Koksal et al., *J Biol Chem*, 2009; Koksal and Cingolani, *J Biol Chem*, 2011), the p53-phosphatase DUSP26 (Lokareddy et al., *Biochemistry*, 2013), the 5'-RNA-phosphatase PIR1 (Sankhala et al., *Biochemistry*, 2014) and the glycogen phosphatase laforin (Sankhala et al., *J Biol Chem*, 2015). The long-term work of this work is to decipher the molecular determinants that make DSPs substrate-specific *in vivo*. In the case of multi-domain phosphatases like laforin, we seek to understand how phosphatase activity is regulated in the context of

the full-length enzyme. This is essential to develop new 'smart' drugs that selectively interfere with substrate recognition, as opposed to catalytic activity. Key publications in this field include:

e. Koksal, A., Nardozzi, J., and **Cingolani, G.** (2009) Dimeric quaternary structure of the prototypical dual-specificity phosphatase VH1. *J. Biol. Chem.* 284(15):10129-37. PMCID: PMC2665067.

f. Lokareddy, K.R., Bhardwaj, A. and **Cingolani, G.** (2013) Atomic structure of DUSP26, a novel p53 phosphatase. *Biochemistry*, 52(5):938-48. PMCID: PMC3619938.

g. Sankhala, S.R., Koksal, C.A., Ho, L., Nitschke, F., Minassian, A.B. and **Cingolani, G.** (2015) Dimeric quaternary structure of human laforin. *J Biol. Chem*. 290(8):4552-559. PMCID: PMC4335197.

h. Florio T., Lokareddy R.K., Gillilan R. and **Cingolani, G.** (2019) Molecular architecture of the inositol phosphatase Siw14. *Biochemistry*. 58(6):534-545. PMCID: PMC6526948

4. Structure and inhibition of bacterial virulence factors. We have a general interest in the structure and enzymatic mechanisms of pathogenesis-related bacterial proteins as novel antibacterial targets. We determined the structure of the Escherichia coli F_1 ATPase core auto-inhibited by epsilon subunit (Cingolani and Duncan, Nature Struc Mol Biol. 2011), which revealed a novel mode of intramolecular regulation of rotary catalysis. In collaboration with Dr. Michael Niederweis at the University of Alabama, we determined the crystal structure of the Mycobacterium tuberculosis Necrotizing Toxin (TNT) in complex with the Immunity factor IFT, at 1.1 Å resolution (Sun et al. Nature Struc Mol Biol. 2011). We also demonstrated that TNT hydrolyzes the essential co-enzyme nicotinamide adenine dinucleotide (NAD^+) in the cytosol of Mtb-infected macrophages. In collaboration with Dr. Paumet at Thomas Jefferson University, we have studied the Chlamydia trachomatis inclusion protein IncA, which is the first example of a bacterial SNARE-like protein mediating homotypic fusion of intracellular inclusions (Cingolani et al., Nature Commun 2019). Our current work focuses on the structural analysis of Mycobacterium tuberculosis outer membrane proteins that harbor catalytic domains and that represent virulence factors. Key publications in this field include:

i. **Cingolani, G.*** and Duncan, T.M. (2011) Structure of the ATP synthase catalytic complex (F1) from Escherichia coli in an auto-inhibited conformation. *Nature Struc Mol Biol.* 18(6):701-7. (* *corresponding authors*) PMCID: PMC3109198

j. Sun, J., Siroy, A., Lokareddy, K.R., Speer, A., Doornbos, K.S., **Cingolani, G.*** and Niederweis, M.* (2015) The tuberculosis necrotizing toxin kills macrophages by hydrolyzing NAD+. *Nature Struc Mol Biol.* 22(9):672-8. (* *corresponding authors*) PMCID: PMC4560639

k. **Cingolani, G.***, McCauley, M., Lobley, A., Bryer, A.J., Wesolowski, J., Greco, D.L., Lokareddy, R.K., Ronzone, E., Perilla, J.R. and Paumet, F.* (2019) Structural basis for the homotypic fusion of chlamydial inclusions by the SNARE-like protein IncA. *Nature Commun.* 10(1):2747. (* *corresponding authors*) PMCID: PMC6588587

l. Mitra, A., Ko, YH., **Cingolani, G.*** and Niederweis, M.* (2019) Heme and hemoglobin utilization by Mycobacterium tuberculosis. *Nature Commun.* 10(1):4260. (* *corresponding authors*) PMCID: PMC6751184

Complete List of Published Work in MyBibliography (90 publications, >5,265 citations, H-index=38):
https://www.ncbi.nlm.nih.gov/myncbi/1-W_e40W70KkG/bibliography/public/

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: White, Simon

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

POSITION TITLE: Assistant 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)	END DATE MM/YYYY	FIELD OF STUDY
University of Hertfordshire, Hatfield, Hertfordshire	BS	07/2005	Applied Biology
University of Leeds, Leeds, West Yorkshire	MS	07/2006	Biosciences
University of Leeds, Leeds, West Yorkshire	PHD	01/2011	Bionanotechnology

A. Personal Statement

I am well placed to pursue the work laid out in this application. I have extensive experience working with different bacteriophages (various actinobacteriophages, see Podgorski et al. 2020, and M13 and MS2 bacteriophages). I have the experience with cryo-electron microscopy needed for success and have six structures deposited in the electron microscopy databank, and I am currently collaborating with others at the University of Connecticut on cryo-electron microscopy data. In the past year I have built de novo models using actinobacteriophage cryoEM maps (all sub 3 angstrom resolution) for seven bacteriophage (to be deposited). I have the experience needed with cryoSPARC and with Phenix for model building.

I am currently in my fourth year at the University of Connecticut as an assistant Professor. I currently supervise five graduate students (three PhD and two masters) and mentored thirteen undergraduate students (five of whom are still in my lab). We have monthly lab meetings where they present their work in a friendly and supportive environment. These lab meetings are an important tool for trouble shooting problems they may have and developing new avenues of research. They are an excellent team and we are well placed complete the stated aims.

1. Luque A, Benler S, Lee D, Brown C, White S. The Missing Tailed Phages: Prediction of Small Capsid Candidates. Microorganisms. 2020 December 08; 8(12):1944-. Available from: https://www.mdpi.com/2076-2607/8/12/1944 DOI: 10.3390/microorganisms8121944
2. Podgorski J, Calabrese J, Alexandrescu L, Jacobs-Sera D, Pope W, Hatfull G, White S. Structures of Three Actinobacteriophage Capsids: Roles of Symmetry and Accessory Proteins. Viruses. 2020 March 08; 12(3):294. Available from: https://www.mdpi.com/1999-4915/12/3/294/htm DOI: 10.3390/v12030294
3. Shakeel S, Dykeman EC, White SJ, Ora A, Cockburn JJB, Butcher SJ, Stockley PG, Twarock R. Genomic RNA folding mediates assembly of human parechovirus. Nat Commun. 2017 Feb 23;8(1):5. PubMed Central PMCID: PMC5431903.
4. White SJ, Johnson S, Szymonik M, Wardingley RA, Pye D, Davies AG, Wälti C, Stockley PG. Directed surface attachment of nanomaterials via coiled-coil-driven self-assembly. Nanotechnology. 2012 Dec 14;23(49):495304. PubMed Central PMCID: PMC4785676.

B. Positions and Honors

Positions and Employment

2017 - Assistant Professor, UNIVERSITY OF CONNECTICUT
2010 - 2017 Post doctoral research assistant, UNIVERSITY OF LEEDS

Other Experience and Professional Memberships

2018 - Member, American Society for Virology

Honors

2016 Best Poster Award at FASEB: Virus Structure and Assembly, FASEB
2016 Best Poster Award at the Astbury Conversation Symposium, University of Leeds
2016 The Dean's Vacation Research Scholarship, University of Leeds
2015 Award for Outstanding Contribution (Oral Presentation) at the XXIV Biennial Conference on Phage/Virus Assembly, Phage and Virus Assembly
2006 Award for Best Result in Year Group, University of Leeds
2005 Award for Best Result in Year Group, University of Hertfordshire

C. Contribution to Science

1. I was a PDRA at Leeds University for 5 years, working with Professor Peter Stockley, investigating the assembly mechanisms of positive sense-single stranded RNA viruses. My PDRA work has been instrumental in the discovery, characterisation and validation of a completely unsuspected aspect of the assembly mechanisms in this class of RNA viruses. It appears that they all use an evolutionarily conserved mechanism to ensure survival of the virion in the challenging environment of the infected cell. Our recent discovery of this mechanism in a picornavirus forces a re-examination of decades of research that showed that they did not exist in this family of viruses. These discoveries lead naturally to potential real world applications, including the development of novel antiviral therapies and the creation of artificial and completely safe viral vaccines.

   The work to identify packaging signals in human pathogens (human parechovirus, hepatitis B and C) had a major collaborative association with Prof. Reidun Twarock at the University of York (Department of Mathematics, Centre for Complex Systems Analysis). It features in high impact papers, which have been published in Nature Communications (Shakeel, Dykeman and White [joint first authors], et al.) and Nature Microbiology (Patel and White [joint first authors], et al.). It was an important corner-stone of a patent on a novel anti-viral strategy (jointly held by the Universities of York, Leeds and Helsinki, US20160326529), for which I am a co-inventor, and a Wellcome Trust Joint Senior Investigator Grant to Profs. Stockley and Twarock as well as a grant from the Medical Research Council for which I was named post-doc. The Nature Communications paper received widespread media coverage and resulted in 32 news articles, including articles in CNN and ABC. Likewise, the Nature Microbiology paper resulted in 7 news articles, a “Behind the paper” article in Nature Microbiology, a specific article in Nature Reviews Microbiology discussing the work (York, A. (2017). Viral Infection: Packing to Leave. Nature Reviews Microbiology. 15: 450-451) and three cryo-electron microscopy structures (in which I did the reconstructions) deposited in the electron microscopy data bank (EMDB-3714, EMDB-3715 and EMDB-3716).

   My other work on packaging signals has focused on one of the model systems for viral assembly: the bacteriophage MS2. Working with Prof. Reidun Twarock (York University) and Prof. Cheng Kao (Indiana University), I was part of the team that identified the 60 coat protein:RNA contacts in MS2, the first time that all of the packaging signals have been identified within a virus (see Direct Evidence for Packaging Signal-Mediated Assembly of Bacteriophage in JMB). Our work was the focus of a review by Peter Prevelige (Follow the Yellow Brick Road: A paradigm Shift in Virus Assembly, 2016, Journal of Molecular Biology, 428: 416-418) which highlights the importance of my work. The entire field of (+)ssRNA viruses must now revisit existing mechanisms of assembly in the light of our work and I expect many groups to start exploring packing signals in other (+)ssRNA viruses.

   a. Patel N, White SJ, Thompson RF, Bingham R, Weiß EU, Maskell DP, Zlotnick A, Dykeman E, Tuma R, Twarock R, Ranson NA, Stockley PG. HBV RNA pre-genome encodes specific motifs that mediate interactions with the viral core protein that promote nucleocapsid assembly. Nat Microbiol. 2017 Jun 19;2:17098. PubMed Central PMCID: PMC5495169.

b. Shakeel S, Dykeman EC, White SJ, Ora A, Cockburn JJB, Butcher SJ, Stockley PG, Twarock R. Genomic RNA folding mediates assembly of human parechovirus. Nat Commun. 2017 Feb 23;8(1):5. PubMed Central PMCID: PMC5431903.

c. Stewart H, Bingham RJ, White SJ, Dykeman EC, Zothner C, Tuplin AK, Stockley PG, Twarock R, Harris M. Identification of novel RNA secondary structures within the hepatitis C virus genome reveals a cooperative involvement in genome packaging. Sci Rep. 2016 Mar 14;6:22952. PubMed Central PMCID: PMC4789732.

d. Rolfsson Ó, Middleton S, Manfield IW, White SJ, Fan B, Vaughan R, Ranson NA, Dykeman E, Twarock R, Ford J, Kao CC, Stockley PG. Direct Evidence for Packaging Signal-Mediated Assembly of Bacteriophage MS2. J Mol Biol. 2016 Jan 29;428(2 Pt B):431-48. PubMed Central PMCID: PMC4751978.

2. I have made contributions to the field of bio-nanoscience, exploring bio-templated device construction in collaboration with Profs. Giles Davies and Christoph Wälti at the University of Leeds and Dr. Steve Johnson at the University of York. This utilized the M13 bacteriophage displaying coiled-coil motifs to specifically assemble the phage particle between two electrodes. This work culminated in the publication in the high impact journal of Angewandte Chemie studying the structure and assembly of coiled-coils on a 2-D surface. I showed that the assembly of coiled-coils on a surface results in molecular crowding and results in the properties of the coiled-coil changing, i.e. the pH at which they assemble/disassemble is radically changed when crowded onto a 2D surface, as compared to solution. This work has important implications for various 2-D surface techniques, e.g. surface plasmon resonance, and bio-nano diagnostic devices. It has been cited 9 times. The work is continuing using the B23 (circular dichroism) beamline at the diamond light source to study the control of coiled-coil interactions using voltage controlled electrodes with the aim of making a switchable surface for the capture and release of various biological molecules, e.g. specific cell types in cell sorting applications.

   a. White SJ, Johnson SD, Sellick MA, Bronowska A, Stockley PG, Wälti C. The influence of two-dimensional organization on peptide conformation. Angew Chem Int Ed Engl. 2015 Jan 12;54(3):974-8. PubMed Central PMCID: PMC4506555.

   b. White SJ, Johnson S, Szymonik M, Wardingley RA, Pye D, Davies AG, Wälti C, Stockley PG. Directed surface attachment of nanomaterials via coiled-coil-driven self-assembly. Nanotechnology. 2012 Dec 14;23(49):495304. PubMed Central PMCID: PMC4785676.

   c. White SJ, Morton DW, Cheah BC, Bronowska A, Davies AG, Stockley PG, Wälti C, Johnson S. On-surface assembly of coiled-coil heterodimers. Langmuir. 2012 Oct 2;28(39):13877-82. PubMed Central PMCID: PMC4820041.

3. I have used SELEX to identify many novel RNA aptamers which have played an important role in the development of biosensors. The first set of aptamers was involved in the detection of the aminoglycoside antibiotics in collaboration with FERA (Food and Environment Research Agency) in the U.K. who wanted to develop a cheap and quick biosensor for the detection of aminoglycoside antibiotics in milk. Aptamers were discovered that could be used in an assay and detect the antibiotics in the nM range. The second set of RNA aptamers that I developed was for the differentiation between different conformations of amyloid precursors. I successfully identified aptamers that could achieve this.

   a. Sarell CJ, Karamanos TK, White SJ, Bunka DHJ, Kalverda AP, Thompson GS, Barker AM, Stockley PG, Radford SE. Distinguishing closely related amyloid precursors using an RNA aptamer. J Biol Chem. 2014 Sep 26;289(39):26859-26871. PubMed Central PMCID: PMC4175327.

   b. Derbyshire N, White SJ, Bunka DH, Song L, Stead S, Tarbin J, Sharman M, Zhou D, Stockley PG. Toggled RNA aptamers against aminoglycosides allowing facile detection of antibiotics using gold nanoparticle assays. Anal Chem. 2012 Aug 7;84(15):6595-602. PubMed Central PMCID: PMC3413241.

D. Scholastic Performance

Ongoing Research Support

Start-up grant, University of Connecticut
White, Simon (PI)
08/23/17-08/23/22
Department Start-up grant.
The purpose of this grant is to set up the PI's laboratory, as well as a facility for cryoEM sample preparation. To be used to fund preliminary studies needed to be competitive for extramural research support
Role: PI

1 R21 AI156838-01, NIH
White, Simon (PI)
12/01/20-11/30/22
Characterization of long-circulating phages isolated from in vivo mouse studies
Role: PI

Completed Research Support

17-EXO17_2-0063, NASA
White, Simon (PI)
04/01/18-03/31/21
Characterizing the molecular mechanisms and the limits of archaeal gene transfer using Haloferax volcanii as a model genetic system
Though archaea are largely unexplored for horizontal gene transfer mechanisms, the model archaeon Haloferax volcanii has demonstrated a cell-cell contact mediated DNA transfer mechanism involving cell fusion events that generate a 1N/2N/1N chromosome copy number cycle. This mechanism leads to the recombination of DNA, and changes their genotype and phenotype. How this mechanism functions in the genetically tractable Haloferax volcanii is still not understood and many of the features remain elusive. The following specific aims/objectives are proposed to delve deeper into the ambiguities! 1) Identify and characterize components required for cell-cell contact mediated gene exchange (mating) in Haloferax volcanii. 2) Identify and characterize components of a homoserine lactone based quorum sensing system in Haloferax volcanii. 3) Characterize the limits to HGT via mating in Hfx. volcanii.
Role: Co-Investigator

AIMS, ATOMWISE AIMS AWARD
White, Simon (PI)
05/31/18-05/31/20
EV71 2C as a drug target
The EV71 crystal structure was used to identify 72+ compounds identified with a customized small molecule virtual screen using Atomwise's AI technology. Atomwise ship these compounds to the researcher for testing in a malachite green ATPase assay.
Role: PI

Research Excellence Program, Internal funding
White, Simon (PI)
06/30/19-06/30/20
Understanding the role of non-coding RNA in the Picornavirus life-cycle

Undertake next-generation sequencing of cells infected with Picornaviruses to identify common non-coding RNAs differentially expressed during infection
Role: PI

Program in Accelerated therapeutics for healthcare trailblazer award, Internal funding
White, Simon (PI)
06/30/19-06/30/20
Screening for small molecule inhibitors against Enterovirus D68 2C helicase
Identify small molecule inhibitors that specifically inhibit the conserved 2C helicase of EVD68
Role: PI

Program in Innovative Therapeutics for Connecticut's Health (PITCH) program, Internal
White, Simon (PI)
05/01/19-04/01/20
The Picornavirus 2C as a drug target
Developing novel anti-virals against human rhinovirus and enterovirus 71.
Role: PI

Scholarship Facilitation Fund, Internal funding
White, Simon (PI)
01/02/19-01/02/20
Understanding viral evolution through structural analysis
Use cryo-EM to analyze the major capsid proteins of related bacteriophage that infect the Actinobacteria
Role: PI