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: Muir, Tom

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

POSITION TITLE: Van Zandt Williams, Jr. Class of ’65 Professor of Chemistry, Department of Chemistry

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 Edinburgh, Edinburgh, Edinburgh	BS	05/1989	Chemistry (1st Honors)
University of Edinburgh, Edinburgh, Edinburgh	PHD	01/1993	Organic Chemistry
The Scripps Research Institute, San Diego, CA	OTH	12/1995	Postdoc - Bio-organic Chemistry

A. Personal Statement

In the Muir Lab, we have developed general protein engineering approaches that allow recombinant polypeptides and synthetic polypeptides (or other artificial molecules) to be ligated together through a normal peptide bond. This technology, which can be applied both in vitro and in vivo, opens up the world of proteins to the tools of organic chemistry by allowing the insertion of unnatural amino acids, posttranslational modifications and isotopic probes site-specifically anywhere into proteins. Our methods are now used by numerous laboratories worldwide, and have allowed a large number of questions to be addressed. Of particular relevance to the current proposal is our work on chromatin biology. Over the last several years, we have developed a suite of chemistry-driven methods to study how post-translational modifications of the core histone proteins in chromatin regulate the structure and function of the chromatin fiber. This has led to new insights into the flow and storage of epigenetic information in mammalian cells, information that has improved our understanding of the molecular basis of fundamental DNA-templated processes such as transcription and that suggests new routes for the treatment of human diseases, many of which have an epigenetic origin.

My lab provides a unique and exemplary training experience for young scientists to pursue their research. We offer superb research facilities and equipment for the production of proteins and chromatin via protein semisynthesis. Other projects include exploration of the enzymology and mechanisms of inteins using semisynthetic and NMR approaches, understanding the molecular mechanisms including molecular recognition processes underlying the Agr quorum sensing circuit controlling virulence in Staphylococci, investigation of the role of histidine phosphorylation in eukaryotic cells, and the use of genetic and chemical biology methods to study and modify, for the purposes of protein engineering, intein protein splicing elements. Our lab offers an extremely collaborative spirit both within as well as with other research groups. I have a strong history of mentoring young scientists and training graduate students and postdocs. The Muir lab has trained a large number of predoctoral and postdoctoral candidates, and all have gone on to successful independent careers. In total, there have been over 57 pre- and-postdoctoral candidates that have come through the Muir lab, with many (currently 22) having assumed independent academic positions. To date, I have trained 26 PhD students (of whom 12 are women) and 31 postdoctoral fellows (of whom 11 are women). These individuals have obtained positions in industry and at leading academic institutions around the world.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023 -	Guest Investigator, ROCKEFELLER UNIVERSITY, New York, NY
2021 - 2021	Scientific Review Subcommittee, MRC Laboratory of Molecular Biology, PNAC Division, Cambridge
2020 -	Scientific Advisory Board Member, Camille and Henry Dreyfus Foundation, Inc., New York, NY
2020 -	Scientific Advisory Committee, Institute for Molecular Biosciences, Brisbane
2019 -	Scientific Advisory Committee, Rosalind Franklin Institute, Oxford
2017 -	External Scientific Consultant, Fenwick and West LLP
2016 – 2016	Scientific Review Subcommittee, MRC Laboratory of Molecular Biology, PNAC Division, Cambridge
2015 - 2020	Chair, Department of Chemistry, PRINCETON UNIVERSITY, Princeton, NJ
2015 -	External Scientific Consultant, Merck, Sharp & Dohme Corporation, Kenilworth, NJ
2015 - 2021	Scientific Advisory Board Member, Alfred P. Sloan Foundation, New York, NY
2014 -	Co-Founder & Scientific Advisory Board Member, ProteoDesign / SpliceBio, Barcelona
2014 – 2021	Biomedical Scholars National Advisory Committee, The Pew Charitable Trusts, Philadelphia, PA
2014 - 2014	Ad-hoc member, NIH NIGMS Advisory Council, Washington, DC
2012 -	External Advisory Board Member, Institute of Biomedical Research, Barcelona
2012 - 2015	Associate Editor, Chemical Science
2011 -	Van Zandt Williams Jr. Class of ’65 Professor of Chemistry, PRINCETON UNIVERSITY, Princeton, NJ
2010 - 2019	Scientific Advisory Board Member, Redwood Biosciences, Emeryville, CA
2010 – 2016	Member of Scientific Advisory Committee, European Molecular Biology Laboratory, Heidelberg
2010 - 2012	Member of Review Panel, NIH Directors Pioneer Award, NIH
2009 -	Review Panel Member, Center Grants, Swiss National Science Foundation, Bern
2009 - 2015	Council Member, American Peptide Society, Columbus, OH
2008 -	Member Awards Committee, American Peptide Society, Columbus, OH
2005 - 2011	Richard E. Salomon Family Professor /Head of Selma & Lawrence Ruben Laboratory, ROCKEFELLER UNIVERSITY, New York, NY
2005 - 2011	Director, Pels Family Center for Chemistry, Biochemistry and Structural Biology, ROCKEFELLER UNIVERSITY, New York, NY
2005 - 2006	Member Synthetic and Biological Chemistry B Study Section, NIH
2004 – 2007	Member, Review Panel, Damon Runyon Cancer Foundation, New York, NY
2003 - 2005	Member Bioorganic & Natural Product Chemistry Study Section, NIH
2000 - 2002	Associate Professor and Head of the Selma and Lawrence Ruben Laboratory, ROCKEFELLER UNIVERSITY, New York, NY
1996 - 2000	Assistant Professor and Head of Laboratory, ROCKEFELLER UNIVERSITY, New York, NY
1995 - 1996	Senior Research Associate, THE SCRIPPS RESEARCH INSTITUTE, San Diego, CA
1993 - 1995	Postdoctoral Associate, THE SCRIPPS RESEARCH INSTITUTE, San Diego, CA

Honors

2021	Elected Fellow, The Royal Society of London
2020	Ira Remsen Award, American Chemical Society, Maryland Section
2020	Elected Fellow, The American Academy of the Arts and Sciences
2017	E.T. Kaiser Award in Protein Chemistry, The Protein Society
2016	Breslow Award in Biomimetic Chemistry, American Chemical Society
2013	Arthur C. Cope Scholar Award, American Chemical Society
2013	Elected Fellow, The Royal Society of Edinburgh
2012	Jeremy Knowles Award, Royal Society of Chemistry
2012	MERIT Award, US National Institutes of Health, NIGMS
2012	Elected Fellow, The Royal Society of Chemistry
2008	Vincent du Vigneaud Award in Peptide Chemistry, American Peptide Society

2008 Distinguished Teaching Award, Rockefeller University
2008 Blavatnik Award for Young Scientists and Engineers, New York Academy of Sciences
2007 Elected Fellow, The American Association for the Advancement of Science
2005 Irving Sigal Young Investigator Award, The Protein Society
2002 Leonidas Zervas Award, European Peptide Society
2001 Irma T. Hirschl/Monique Weill-Caulier Trust Research Fellow
2000 Alfred P. Sloan Research Fellow
1999 Burroughs-Wellcome Fund New Investigator Award
1998 Pew Scholar in the Biomedical Sciences

C. Contributions to Science

1. The Regulation of Chromatin Structure and Function: We have developed a suite of chemistry-driven methods to study how post-translational modifications of the core histone proteins in chromatin regulate the structure and function of the chromatin fiber. This has led to new insights into the flow and storage of epigenetic information in mammalian cells, information that has improved our understanding of the molecular basis of fundamental DNA-templated processes such as transcription and that suggests new routes for the treatment of human diseases, many of which have an epigenetic origin. Some relevant papers are listed below.

    a. Mashtalir N, Dao HT, Sankar A, Liu H, Corin AJ, Bagert JD, Ge EJ, D'Avino AR, Filipovski M, Michel BC, Dann GP, Muir TW, Kadoch C. Chromatin landscape signals differentially dictate the activities of mSWI/SNF family complexes. Science. 2021 Jul 16;373(6552):306-315. PubMed Central PMCID: PMC8390793.
    b. Bagert JD, Mitchener MM, Patriotis AL, Dul BE, Wojcik F, Nacev BA, Feng L, Allis CD, Muir TW. Oncohistone mutations enhance chromatin remodeling and alter cell fates. Nat Chem Biol. 2021 Apr;17(4):403-411. PubMed Central PMCID: PMC8174649.
    c. Dann GP, Liszczak GP, Bagert JD, Müller MM, Nguyen UTT, Wojcik F, Brown ZZ, Bos J, Panchenko T, Pihl R, Pollock SB, Diehl KL, Allis CD, Muir TW. ISWI chromatin remodellers sense nucleosome modifications to determine substrate preference. Nature. 2017 Aug 31;548(7669):607-611. PubMed Central PMCID: PMC5777669.
    d. McGinty RK, Kim J, Chatterjee C, Roeder RG, Muir TW. Chemically ubiquitylated histone H2B stimulates hDot1L-mediated intranucleosomal methylation. Nature. 2008 Jun 5;453(7196):812-6. PubMed Central PMCID: PMC3774535.

2. Structure and Function of Inteins: Protein splicing is a remarkable posttranslational process in which an intervening sequence, termed an intein, becomes excised from a host protein, the extein, in an autocatalytic manner. In protein trans-splicing the intein is split into two pieces and splicing only occurs upon reconstitution of these fragments. We have for many years studied the molecular details of protein splicing that occurs in cis and in trans. Indeed, through our efforts, and those of others, we now have a much clearer picture of the nature of catalysis for all the steps in the canonical protein splicing mechanism. In addition, new technologies have emerged from these basic mechanistic studies, and these have been used to answer a number of biology questions.

    a. Gramespacher JA, Burton AJ, Guerra LF, Muir TW. Proximity Induced Splicing Utilizing Caged Split Inteins. J Am Chem Soc. 2019 Sep 4;141(35):13708-13712. PubMed Central PMCID: PMC6903685.
    b. Thompson RE, Stevens AJ, Muir TW. Protein engineering through tandem transamidation. Nat Chem. 2019 Aug;11(8):737-743. PubMed Central PMCID: PMC6711197.
    c. Gramespacher JA, Stevens AJ, Nguyen DP, Chin JW, Muir TW. Intein Zymogens: Conditional Assembly and Splicing of Split Inteins via Targeted Proteolysis. J Am Chem Soc. 2017 Jun 21;139(24):8074-8077. PubMed Central PMCID: PMC5533455.
    d. Shah NH, Dann GP, Vila-Perelló M, Liu Z, Muir TW. Ultrafast protein splicing is common among cyanobacterial split inteins: implications for protein engineering. J Am Chem Soc. 2012 Jul 18;134(28):11338-41. PubMed Central PMCID: PMC3535263.

3. Protein Chemistry in Living Cells and Animals: We have for several years explored the possibility of performing protein chemistry inside living systems – in principle this would allow for protein structure and function to be controlled and manipulated in ways inaccessible to standard genetics. A number of technologies have emerged from this initiative – many of which have relied on insights emerging from our long-standing mechanistic studies of inteins, remarkable proteins which mediate protein splicing (a naturally occurring protein editing reaction). These include a variety of small molecule and optically controlled protein ligation reactions, which permit the spatial-temporal control of protein function in cells and living animals. Key papers are listed below.

    a. Burton AJ, Haugbro M, Parisi E, Muir TW. Live-cell protein engineering with an ultra-short split intein. Proc Natl Acad Sci U S A. 2020 Jun 2;117(22):12041-12049. PubMed Central PMCID: PMC7275667.
    b. Burton AJ, Haugbro M, Gates LA, Bagert JD, Allis CD, Muir TW. In situ chromatin interactomics using a chemical bait and trap approach. Nat Chem. 2020 Jun;12(6):520-527. PubMed Central PMCID: PMC7331920.
    c. Liszczak GP, Brown ZZ, Kim SH, Oslund RC, David Y, Muir TW. Genomic targeting of epigenetic probes using a chemically tailored Cas9 system. Proc Natl Acad Sci U S A. 2017 Jan 24;114(4):681-686. PubMed Central PMCID: PMC5278450.
    d. David Y, Vila-Perelló M, Verma S, Muir TW. Chemical tagging and customizing of cellular chromatin states using ultrafast trans-splicing inteins. Nat Chem. 2015 May;7(5):394-402. PubMed Central PMCID: PMC4617616.

4. Virulence Regulation in Staphyloccus Aureus: In a separate area of work, we have worked for many years to understand the molecular details of virulence control in pathogenic Staphylococci. We have defined the molecular structure of a family of secreted peptides from S. aureus that control virulence in the organism through a conserved quorum sensing signaling pathway termed agr. Agr remains the best-characterized quorum sensing pathway in any Gram-positive organism and, given its biomedical importance, is now widely studied. Using a combination of chemistry, protein engineering and molecular genetics, we have figured out many aspects of the molecular mechanism of this critical process. This understanding has led to the rational design of global inhibitors of virulence in S. aureus that prevent infections in animal models and that thus have therapeutic potential. Key contributions are listed below.

    a. Xie Q, Zhao A, Jeffrey PD, Kim MK, Bassler BL, Stone HA, Novick RP, Muir TW. Identification of a Molecular Latch that Regulates Staphylococcal Virulence. Cell Chem Biol. 2019 Apr 18;26(4):548- 558.e4. PubMed Central PMCID: PMC6506218.
    b. Wang B, Zhao A, Novick RP, Muir TW. Activation and inhibition of the receptor histidine kinase AgrC occurs through opposite helical transduction motions. Mol Cell. 2014 Mar 20;53(6):929-40. PubMed Central PMCID: PMC4004102.
    c. Kee JM, Oslund RC, Perlman DH, Muir TW. A pan-specific antibody for direct detection of protein histidine phosphorylation. Nat Chem Biol. 2013 Jul;9(7):416-21. PubMed Central PMCID: PMC3686892.
    d. Mayville P, Ji G, Beavis R, Yang H, Goger M, Novick RP, Muir TW. Structure-activity analysis of synthetic autoinducing thiolactone peptides from Staphylococcus aureus responsible for virulence. Proc Natl Acad Sci U S A. 1999 Feb 16;96(4):1218-23. PubMed Central PMCID: PMC15443.