BIOGRAPHICAL SKETCH

NAME: Swairjo, Manal A.

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

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Kuwait University	B.S	05/1988	Physics & Mathematics
Boston University, Massachusetts	Ph.D.	05/1996	Cellular Biophysics
GlaxoSmithKline	Postdoctoral	08/1998	Structural Biology

A. Personal Statement

The goal of the proposed research is to elucidate the molecular basis for the recently discovered 7-deazaguanine base modifications in DNA, and characterize functionally, mechanistically and structurally the enzyme system responsible for the modification and which represent the largest and most complex restriction-modification system known to date. The proposal builds on an established, 15-year tripartite collaboration between Dirk Iwata-Reuyl, Valerie de Crécy-Lagard and myself, a collaboration that led to the discovery and full functional, structural, and mechanistic characterization of several enzymes in the biosynthetic pathways to the 7-deazaguanosine modified nucleosides of tRNA queuosine and archaeosine, among other tRNA modification enzymes. Dirk and I published 13 papers together, and Valerie and I published 11 papers together on these systems, and some of the hypotheses addressed in this proposal emerged in part from the crystal structure of Salmonella DpdA enzyme recently determined in my lab as part of these collaborations. My background includes training in structural biology and cellular biophysics and X-ray crystallography at Boston University School of Medicine as a graduate student, and in structure-based drug discovery at GlaxoSmithKline as a postdoctoral scientist. I later led a crystallography research program in the laboratory of Paul Schimmel at The Scripps Research Institute, focusing on molecular evolution of aminoacyl-tRNA synthetases and other tRNA biogenesis proteins. I initiated my research program in the structural biology and biochemistry of tRNA modifications 15 years ago, and I have extensive experience in protein and nucleic acid biochemistry, macromolecular crystallography, structural enzymology, and structural bioinformatics; and have a demonstrated record of success in the structural and mechanistic characterization of complex enzyme systems.

B. Positions and Honors

Positions and Employment

1991-1995 Graduate Research Assistant, Boston University School of Medicine, Dept. of Physiology.
1995-1996 Postdoctoral Fellow, Boston University School of Medicine, Dept. of Physiology.
1996-1998 Postdoctoral Scientist, SmithKline Beecham Pharmaceuticals, Dept. of Structural Biology.
1998-2003 Senior Research Associate, The Scripps Research Institute, La Jolla, CA.
2003-2006 Staff Scientist, The Scripps Research Institute, La Jolla, CA.
2006-2008 Assistant professor, Western University of Health Sciences, Pomona CA.
2008-2010 Adjunct assistant professor, Sanford-Burnham Medical Research Institute, La Jolla CA.
2010-2015 Assistant Professor, Western University of Health Sciences, Pomona CA.
2015-2024 Associate Professor of Biochemistry, San Diego State University, San Diego CA.
2024-present Professor of Biochemistry, San Diego State University, San Diego CA.

Other Experience and Professional Memberships

1996-present	American Crystallographic Association, member.
1996-present	American Chemical Society, member.
2000	Committee of organizers, The Paul Schimmel Symposium, TSRI.
2006	Committee of organizers, International Conference on Aminoacyl-tRNA Synthetases, San Diego, CA.
2008-present	Association for Women in Science, member.
2006-present	Peer reviewer for JBC, EMBO J, eLife, NAR, FEBS Lett., J. Mol. Evol., JMB, etc.
2015	Session co-chair, American Crystallographic Association Annual Meeting, Philadelphia PA
2015-present	The RNA Society, member
2015-present	The American Society for Biochemistry and Molecular Biology, member.
2017-present	Peer reviewer for NIH.

Honors

1990	NATO Award to Photobiological Techniques Advanced Study Institute.
1994	Boston University School of Medicine Graduate Student Meritorious Recognition Award.
1995	Boston University School of Medicine Henry I. Russek Award.
1997	National Research Service Award, NIH.
2007	Beckman Coulter Community Relations Award for mentorship of undergraduate research.
2014	Outstanding Faculty Mentor Award, WesternU.
2015	Best Mentor Award, WesternU.
2021	Quest for the Best Excellence in Mentorship Award, SDSU.
2023	Outstanding Faculty Award, College of Sciences, SDSU.

C. Contributions to Science

1. New chemistry in the biosynthesis of the 7-deazaguanosine modified nucleosides of tRNA and DNA. My research program since 2010 has focused on combining biochemistry, structural biology and structural bioinformatics to discover and characterize the biosynthesis pathways to the 7-deazaguanosines modified nucleosides of transfer-RNA and DNA in bacteria, and their salvage in eukaryotes. This work led to discovery of chemical reactions unprecedented in biology such as nitrile reduction and amidation, and enzymes with novel catalytic mechanisms such as the prokaryotic-specific GTP cychlohydrolase IB. queuosine and archaeosine. My scholarship and collaborations in this area contributed to the growth of the nucleoside modification field.

- Gedara, S., Wood, E., Gustafson, A., Liang, C., Hung, S.-H., Savage, J., Phan, P., Luthra, A., de Crécy-Lagard, V., Dedon, P., **Swairjo, M.A.** and Iwata-Reuyl, D. (**2023**). 7-Deazaguanines in DNA: functional and structural elucidation of a DNA modification system. *Nucl. Acids Res.* 51(8): 3836-3854. (PMID: 36928176, PMCID: PMC10164549).
- Hung, S.-H., Elliott, G.I., Ramkumar, T.R., Burtnyak, L., McGreneghan, C., Alkuzweny, S., Quaiyum, S., Iwata-Reuyl, D., Pan, X., Green, B.D., Kelly, V.P., de Crécy-Lagard, V., and **Swairjo, M.A.** (**2023**). Structural basis of Qng1-mediated salvage of the micronutrient queuine from queuosine-5′-monophosphate as the biological substrate. *Nucl. Acids Res.* 51: 935-951. (PMID: 36610787, PMCID: PMC9881137)
- Kot, W., Olsen, N., Nielsen, T.K., Hutinet, G., de Crecy-Lagard, V., Cui, L., Dedon, P.C. Carstens, A.B., Moineau, S. **Swairjo, M.A.** and Lars H. Hansen. **(2020)**. Detection of $preQ_0$ deazaguanine modifications in bacteriophage CAjan DNA using Nanopore sequencing reveals same hypermodification at two distinct DNA motifs. *Nucl. Acids Res*. (PMID: 32941607, PMCID: PMC7544227).
- Mei, X., Alvarez, J., Bon Ramos, A., Samanta, U., Iwata-Reuyl, D., **Swairjo, M.A.** (**2016**). Crystal structure of the archaeosine synthase QueF-Like – insights into amidino transfer and tRNA recognition by the tunnel fold. *Proteins: Structure, Function, and Bioinformatics*. 85(1):103-116. Cover article. (PMID: 27802572, PMCID: PMC5167649).

- Chikwana V.M., Stec B., Lee B.W., de Crécy-Lagard V, Iwata-Reuyl D, **Swairjo M.A.** (**2012**). Structural basis of biological nitrile reduction. *J. Biol. Chem.*, 287(36):30560-70 (PMID: 22787148, PMCID: PMC3436371).

2. Discovery and characterization of GTP cyclohydrolase IB (GCYH-IB). As part of the search for the enzymes responsible for the biosynthesis of the 7-deazaguanosine modified nucleosides of tRNA, my lab took part in the discovery of the prokaryotic-specific GCYH-IB as the first enzyme in the pathway and as an alternative GTP cyclohydrolase I present in bacteria that lacked the canonical enzyme. My group determined the crystal structure of the enzyme and its novel mechanism of action in which a post-translational S-nitrosyl modification participates in catalysis. These findings paved the way for developing this enzyme as an antibacterial target. The structure-based design of selective guanosine analog inhibitors of GCYH-IB is the subject of a current project in my lab.

- Samaan, G.N., Paranagama, N., Haque, A., Hecht, D.A., **Swairjo, M.A.**, Purse., B.W. **(2020).** Structure-based design of guanosine analogue inhibitors targeting GTP cyclohydrolase IB towards a new class of antibiotics. *Bioorganic & Medicinal Chemistry Letters* 30(2):126818. (PMID: 31771800 PMCID: PMC6942202)
- Paranagama, N., Bonnett, S.A., Alvarez, J., Luthra, A., Stec, B., Gustafson, A., Iwata-Reuyl, D., and **Swairjo, M.A. (2017)**. Mechanism and catalytic strategy of the prokaryotic specific GTP cyclohydrolase IB. *Biochemical Journal,* 474 1017–1039. (PMID: 28126741, PMCID: PMC5558430).
- Sankaran, B., Bonnett, S., Shah, K., Gabriel, S., Reddy, R., Schimmel, P., Rodionov, D.A., de Crécy-Lagard, V., Helmann, J.D., Iwata-Reuyl, D., and **Swairjo, M.A. (2009)**. Zinc-independent folate biosynthesis: genetic, biochemical, and structural investigation reveal new metal dependence for GTP cyclohydrolase IB. *J. Bacteriology*, 191(22): 6936–49. (PMID: 19767425, PMCID: PMC2772490).
- El Yacoubi, B., Bonnett, S., Anderson, J.N., **Swairjo, M.A.**, Iwata-Reuyl, D., and de Crécy-Lagard, V. **(2006)**. Discovery of a new prokaryotic type I GTP cyclohydrolase family. *Journal of Biological Chemistry*, 281(49): 37586–37593. (PMID: 17032654).

3. The biosynthesis of threonylcarbamoyladenosine (t^6A_{37}). The anticodon stem and loop domain (ASL) of a tRNA drives accurate and efficient decoding by binding to the mRNA cognate and wobble codons on the ribosome. Modifications of the ASL are the most distinct and chemically complex of all RNA modifications and are required by at least one third of all bacterial tRNA species for cognate and/or wobble codon recognition and translocation. Deficiencies in these modifications cause hereditary human mitochondrial disease, and modified nucleosides serve as sensitive cancer markers. Threonylcarbamoyladenosine (t^6A_{37}) is a modified nucleoside found exclusively at position 37 in tRNAs responsible for decoding ANN codons (N being any nucleotide) and is one of the few *universal* complex modifications of the ASL. I took part in the discovery and characterization of the first t^6A biosynthesis enzyme, YrdC, which triggered the elucidation of the full biosynthesis pathway of four essential proteins. Our discovery and structural characterization of the bacterial t^6A pathway revealed astonishingly complex enzyme mechanisms and links to other cellular processes such as cell wall metabolism.

- Luthra, A., Paranagama, N., Swinehart, W., Bayooz, S., Phan, P., Quach, V., Schiffer, J.M., Stec, B., Iwata-Reuyl, D., **Swairjo, M.A. (2019).** Conformational communication mediates the reset step in t^6A biosynthesis. *Nucleic Acids Research* 47(12):6551-6567. (PMID: 31114923, PMCID: PMC6614819).
- Luthra, A., Swinehart, W., Bayooz, S., Phan, P., Stec, B., Iwata-Reuyl, D., **Swairjo, M.A.** (**2018**). Structure and mechanism of a bacterial t^6A biosynthesis system, *Nucleic Acids Research* 46: 1395–1411 (PMID: 29309633, PMCID: PMC5814804).
- Harris, K.A., Jones, V., Bilbille, Y., **Swairjo, M.A.** and Agris, P.F. **(2011)**. YrdC exhibits properties expected of a subunit for a tRNA threonylcarbamoyl transferase. RNA, 17(9):1678-87. (PMID: 21775474, PMCID: PMC3162333).

- El Yacoubi, B., Lyons, B., Cruz, Y., Reddy, R., Nordin, B., Agnelli, F., Williamson, J.R., Schimmel, P., **Swairjo, M.A.** and de Crécy-Lagard, V. **(2009)**. The universal YrdC/Sua5 family is required for the formation of threonylcarbamoyladenosine in tRNA. *Nucleic Acids Research*. 37(9):2894-909. (PMID: 19287007, PMCID: PMC2685093).

4. Aminoacyl-tRNA synthetases and evolution of the genetic code. tRNA is the central molecule of translation and the adapter molecule that links nucleotide triplets with amino acids in the genetic code. In the Schimmel lab at Scripps, I conducted structural and functional analyses of aminoacyl-tRNA synthetases and the versatile and ancient OB-fold protein Trbp as examples of sequence-based and structure-based tRNA recognition systems, respectively. The results uncovered unique recognition at the pseudoknot of tRNA by an ancient protein domain that suggests a role in the early evolution of tRNA from primordial minihelices that resembled the two helical arms of modern tRNA and carried its coding capacities. Interaction with the tRNA anticodon bases constitutes the primary mechanism by which synthetases recognize their cognate tRNAs. For alanyl-tRNA synthetase, however, the key identity determinants are in the acceptor stem of tRNA. An important paradigm in the evolution of the genetic code arises from mitochondrial (mt) alanylation reactions. Mt synthetases are nuclearly encoded and are imported to the mitochondria after their synthesis in the cytosol. Thus, mt and cytosolic synthetases co-exist in the cytosol, though transiently. Over the course of evolution, mutations in one version of a synthetase are permitted by the stability of the other version, resulting in a gradual buildup of ambiguity in its tRNA recognition. To avoid such ambiguity in the genetic code, eukaryotes separated the identities of their cytosolic and mt $tRNA^{Ala}$s by shifting the G:U wobble by one or a few positions in the acceptor stems of mt $tRNA^{Ala}$. As a result, the corresponding enzymes do not aminoacylate each other's substrates. My work uncovered the structural basis of this phenomenon in the *Drosophila melanogaster* system, and completed the structural view of all 20 aminoacylation reactions with the elucidation of the last synthetase structure.

- **Swairjo M.A.** and Schimmel P. Breaking sieve for steric exclusion of a noncognate amino acid from active site of a tRNA synthetase. *Proc. Natl. Acad. Sci. USA.* 2005, 102: 988-93. (PMID:15657145).
- Lovato M.A., **Swairjo M.A.**, Schimmel P. Positional recognition of a tRNA determinant dependent on a peptide insertion. *Molecular Cell.* 2004, 13: 843-51. (PMID: 15053877).
- **Swairjo M.A.,** Otero F.J., Yang X.-L., Lovato M.A., *et al.*, Schimmel P. (**2004**). Alanyl-tRNA synthetase crystal structure and design for acceptor-stem recognition. *Mol. Cell.* 13: 829-41. (PMID: 15053876).
- **Swairjo, M.A.**, Morales A.J., Wang C.-C., Ortiz A.R., & Schimmel P. Crystal Structure of Trbp111: a Structure-Specific tRNA Binding Protein. *EMBO J.* 2000, 19: 6287-98. (PMID: 11101501).

5. Annexin structure, function and membrane interactions. As a graduate student I focused on elucidating the role of annexins in membrane structure and physiology. Annexins were a newly discovered large family of calcium-binding, membrane-associated proteins involved in membrane trafficking and exocytosis in eukaryotic cells. Their mechanisms of action and exact roles in membrane remodeling were largely unknown. Using X-ray crystallography, NMR and electron microscopy, I elucidated the structural basis of the calcium-mediated and phosphatidylserine-targeted membrane recognition by annexin V using X-ray crystallography, and defined its membrane binding properties. These studies provided direct evidence of the calcium bridging mechanism proposed for these peripheral membrane proteins. The binding of annexin V to externalized phosphatidylserine on the surfaces of apoptotic cells has since become the basis of a commercialized detection tool for apoptosis, with important applications in cardiovascular disease. Another outcome of these studies was the development and characterization of a unique model membrane system that allows for detection of protein interactions with individual membrane leaflets by NMR. This tool has since been used by many in the membrane field to detect trans-membrane effects of protein binding.

- **Swairjo M.A.**, Roberts M.F., Campos M.-B. Dedman J.R. & Seaton B.A. Annexin V binding to the outer leaflet of small unilamellar vesicles leads to altered inner-leaflet properties: ^{31}P- and ^{1}H-NMR studies. *Biochemistry.* **1994**, 33: 10944-50. (PMID: 8086411).

- **Swairjo M.A.**, Seaton B.A. & Roberts M.F. Effect of vesicle composition and curvature on the dissociation of phosphatidic acid in small unilamellar vesicles — a ^{31}P-NMR study. *Biochimica et Biophysica Acta.* **1994**, 1191: 354-61. (PMID: 8172921).
- **Swairjo M.A**. and Seaton B.A. Annexin structure and membrane interactions: a molecular perspective. *Annual Reviews of Biophysics and Biomolecular Structure.* **1994**, 23: 193-213. (PMID: 7522665).
- **Swairjo M.A.**, Concha N.O., Kaetzel M.A., Dedman J.R. & Seaton B.A. 20. Ca(2+)-bridging mechanism and phospholipid head group recognition in the membrane-binding protein annexin V. *Nature Structural Biology.* **1995**, 2: 968-74. (PMID: 7583670).

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/1ISCAAyucpj/bibliography/40663358/public/?sort=date&direction=ascending

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

Ongoing Research Support

NIH R01GM146075 (Dirk Iwata Reuyl, PI; Manal A Swairjo, co-I)
August 2022- July 2026
"7-deazaguanines in DNA: mechanism and structure of complex genome modification"
The major goal of this project is to characterize the biochemical pathways leading to deazapurine incorporation in DNA.

NIH 1R01GM110588-06 (Manal A. Swairjo, PI; Dirk Iwata Reuyl, co-I; Valérie de Crécy-Lagard, co-I)
Sept 2021-August 2025
"RNA modification: Mechanism and links to other metabolic pathways."
The major goals of this project are to determine the mechanism of formation and specificity of the tRNA modification t^6A in bacteria, and to investigate the regulatory pathways that link it to other vital cellular processes, specifically cell division and cell wall synthesis.

Completed Research Support

NIH R01GM132254-01 (Valérie de Crécy-Lagard, PI; Manal A. Swairjo, co-I; Juan Alfonso, co-I)
04/01/19 - 12/31/23
"Study of Queuosine Salvage and Function in Eukaryotes; a forgotten micronutrient"
This grant supports work to identify and characterize the molecular mechanisms underlying salvage of the modified tRNA nucleoside queuosine and its derivatives from the gut microbiome, and to define how queuine deficiency affects neuronal metabolism and differentiation.
Role: co-I.

NSF (CHE) (Byron Purse, PI; Manal A. Swairjo, collaborator) 08/01/18 – 7/31/2021
"Next-Generation Fluorescent Nucleosides and Structure-Photophysics Relationships"
This grant supports work to elucidate the structural basis of the photophysical properties of DNA and RNA duplexes containing novel fluorescent nucleosides.
Role: Collaborator.

NIH/NIGMS 1R01GM110588-01 (Manal A. Swairjo, PI; Dirk Iwata-Reuyl & Paul Agris, co-I's)
09/01/2014 - 08/31/2020
"RNA modification: Structure and Mechanism."

This grant supports work to elucidate biochemically and structurally the molecular mechanisms underlying the biosynthesis of the universal modified nucleoside threonylcarbamoyladenosine.
Role: PI. Current application is a renewal of this grant.

NSF (CHE-CLP) (Dirk Iwata-Reuyl, PI; Manal Swairjo, co-I) 07/01/13 – 06/30/17
"Structure and mechanism in an enzyme superfamily"
This grant supports work to elucidate the structures and mechanisms of a functionally divergent set of tunnel-fold enzymes responsible for the biosynthesis of several 7-deazaguanosine-based modified nucleosides of RNA.
Role: Co-PI

Collaborators

Dmitry Lyumkis (Salk Institute), Dirk Iwata-Reuyl (Portland State Univ.), Valérie de Crécy-Lagard (UFl), Steve Reichow (OHSU), Paul Agris (University at Albany, SUNY), Juan Alfonzo (Ohio State University), Vincent Kelly (Trinity College, Ireland), Brian Green (Queen's University, Ireland), Jamie Williamson (TSRI), Peter Dedon (MIT), Lars Hansen (University of Copenhagen), Jamie Schiffer (Schrodinger), Byron Purse (SDSU), Christal Sohl (SDSU), among others.