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: Summers, Michael F.

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

POSITION TITLE: Professor and HHMI Investigator

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date	FIELD OF STUDY
University of West Florida	B.S.	1980	Chemistry
Emory University	Ph.D.	1984	Bioinorganic Chemistry
National Institutes of Health	Postdoc	1984-87	NMR Methodology

A. Personal Statement

My laboratory has worked in the area of biological magnetic resonance spectroscopy for more than 30 years. I have served terms on two NIH study sections, was on the NIH Office of AIDS Research Advisory Council, am presently a member of the NIGMS Advisory Council, and have been continuously NIH funded since 1989 (including 20 years of NIH MERIT support). I have been an HHMI Investigator for more than 25 years and was elected to the National Academy of Sciences in 2016. Our laboratory uses NMR spectroscopy and other biophysical methods to understand the molecular structures and mechanisms associated with HIV assembly and genome packaging. **Mentoring:** I have mentored 42 graduate students (64% women, 40% URM) and 26 postdoctoral fellows (58% women, 35% URM), and 313 undergraduates (58% female, 47% URM). Examples of female postdocs who successfully matriculated to research-intensive faculty positions include Victoria D'Souza (full professor at Harvard), Sepideh Khorasanizadeh (rose to full professor at U. Virginia; now at U. Oxford), Xiao Heng (recently tenured at Missouri-Columbia), and Sarah Keane (tenure-track at Michigan), among others. I direct an HHMI Education grant program at UMBC that supports high-achieving URM undergraduates, and an NIH IMSD-supported program for diversifying our graduate programs, which now supports more than 80 URM PhD students. For my mentoring activities I have received the Ruth Kirschtein Award of the American Society for Biochemistry and Molecular Biology (2014), the Carl Brändén Award of the Protein Society (2011), the American Association for the Advancement of Science (AAAS) Mentor Award (2003), the Emily M. Gray Award for Biophysical Society (2003), and the White House Presidential Award for Science Mentoring (2000). I am strongly committed to a diverse and inclusive lab environment, and details of my approach to mentoring are described in detail in article (2) below.

Publications related to this proposal:

1. Sto. Domingo, M. R., Sharp, S., Freeman, A., Freeman Jr., T., Harmon, K., Wiggs, M., Sathy, V., Panter, A. T., Oseguera, L., Sun, S., Williams, M. E., Templeton, J., Folt, C. L., Barron, E. J., Hrabowski III, F. A., Maton, K. I., Crimmins, M., Fisher, C. R., Summers, M. F. "Replicating Meyerhoff for inclusive excellence in STEM," *Science* **364**, 335-337 (2019).
2. Summers, M. F. "Training the next generation of Protein Scientists," *Protein Science* **20**, 1796-1801 (2011).
3. Summers, M. F., Hrabowski, F. A. III, "Preparing minority scientists and engineers," *Science* **311**, 1870-1871 (2006).

B. Positions and Honors

Positions and Employment

1996-present **Professor**, Department of Chemistry and Biochemistry, University of Maryland Baltimore County; **Adjunct Professor**, University of Maryland at Baltimore
1994-present **Investigator**, Howard Hughes Medical Institute
1987-1996 **Assistant and Associate Professor**, University of Maryland Baltimore County

Other Experiences and Professional Memberships

Chair, Natl. Acad. Sci. Subcommittee on Diversity, Equity and Inclusion (2021-2022)
Associate Editor, *Journal of Molecular Biology* (1999-present)
Editorial Advisory Board, *J. Biomol. NMR* (2000-present)
Advisory Board, Keystone Symposia Minority Affairs (2007-2012)
Minority Affairs Committee, Biophysical Society (2000-2003); FASEB (2006-2012)
ASBMB Minority Affairs Committee (2008-2014)
Council Member, ACS Project SEED (2005-2009)
Advisory Council, NIH Office of AIDS Research (2006-2011)
Editorial Advisory Board, *Protein Science* (1997-2008)
NIH Therapeutics Advisory Committee, Office of AIDS Research (2003-2007)
NIH Etiology, Pathogenesis Advisory Committee, Office AIDS Research (2003-2007)
NSF Education and Human Resources Advisory Committee (2003-2006)
Board of Directors, FASEB (2002-2006)
Chair, Advisory Council, National Magnetic Resonance Facility at Madison (1995-1999)
NIH Study Sections: BBCA (1995-1999), Reviewers Reserve (1990-1995)

Honors

Elected Member, National Academy of Sciences, 2016
Chinese Academy of Sciences International Distinguished Scientist, 2015
Ruth Kirschstein Award of the American Society for Biochemistry and Molecular Biology, 2014
Sigma Xi Distinguished Lecturer, 2011-2013
Carl Brändén Award of the Protein Society, 2011
Elected Fellow, American Association for the Advancement of Science, 2010
ASBMB Award for Exemplary Contributions to Education, 2008
NIH Merit Award (AI30917), 2006-2016
NIH Merit Award (AI30917), 1997-2006
Maryland Chemist of the Year Award, ACS-Maryland Section, 2004
AAAS Mentor of the Year Award, 2003
Emily M. Gray Mentor Award of the Biophysical Society, 2003
William A. Hinton Mentor Award of the American Society for Microbiology, 2002
White House Presidential Award for Science, Engineering and Math Mentoring, 2000
UMBC Presidential Research Professor, 1999-2002
Meyerhoff Mentor Award, 1999
University System of Maryland Regents Award for Excellence in Research, 1998
EAS Award for Achievements in Magnetic Resonance, 1998
Young Investigator Award of the Protein Society, 1996
Maryland Distinguished Young Scientist Award, 1996 and 1994
University of West Florida Distinguished Alumnus Award, 1994

C. Contributions to Science

1. Structure, function, and antiviral targeting of retroviral Nucleocapsid proteins

We demonstrated that conserved arrays of Cys and His residues (CCHC) bind zinc and form a novel class of zinc fingers (1). The relevance of this motif was debated until we showed by EXAFS that the arrays are populated with zinc in intact virions (1,2). We determined 3D structures and dynamical properties of isolated zinc fingers

from a number of different retroviral families, as well as the structures of the intact HIV-1 nucleocapsid protein (NC) that contains two CCHC motifs (1). The structure of the NC complex with a cognate viral hairpin RNA revealed molecular determinants of zinc finger-guanosine recognition and binding (3). We also discovered a novel class of antivirals that function by covalently binding to specific cysteine sulfurs and ejecting zinc (4).

1. Summers, M.F., Henderson, L.E., Chance, M.R., Bess, Jr., J.W., South, T.L., Blake, P.R., Sagi, I., Perez-Alvarado, G., Sowder, III, R.C., Arthur, L.O. "Nucleocapsid Zinc Fingers Detected in Retroviruses: EXAFS Studies of Intact Viruses and the Solution-State Structure of the Nucleocapsid Protein from HIV-1," *Protein Science* **1**, 563-574 (1992).

2. Chance, M.R., Sagi, I., Wirt, M.D., Frisbie, S.M., Scheuring, E., Chen, E., Bess Jr., J.W., Henderson, L.E., Arthur, L.O., South, T.L., Perez-Alvarado, G., Summers, M.F. "EXAFS Studies of a Retrovirus: Equine Infectious Anemia Virus Cysteine Arrays are Coordinated to Zinc," *Proc. Natl. Acad. Sci. U.S.A*. **89**, 10124-10128 (1992).

3. De Guzman, R. N., Wu, Z. R., Stalling, C. C., Pappalardo, L., Borer, P. N., Summers, M. F. "Structure of the HIV-1 Nucleocapsid Protein Bound to the SL3 □-RNA Recognition Element," *Science* **279**, 384-388 (1998).

4. Rice, W.G., Schaeffer, C.A., Harten, B., Villinger, F., South, T.L., Summers, M.F., Henderson, L.E., Bess, Jr., J.W., Arthur, L.O., McDougal, J.S., Orloff, S.L., Mendeleyev, J., Kun, E. "Inhibition of HIV-1 infectivity by zinc-ejecting aromatic C-nitroso compounds," *Nature* **361**, 473-475 (1993).

2. Structure and function of retroviral Matrix proteins

We determined the 3D structures of several unmyristylated retroviral matrix (MA) proteins (e.g, see (1,2)). MA comprises the domain of the immature Gag protein, and directs intracellular trafficking and membrane targeting for virus assembly. We then developed a dual expression system that enabled us to prepare and characterize the N-terminally myristylated forms of the HIV-1, HIV-2 and Feline Immunodeficiency Virus (FIV) MA proteins (e.g, see (3)). We showed that trafficking to assembly sites is mediated by direct MA interactions with phosphatidylinositol-4,5-bisphosphate (PIP2), a cellular factor considered to function as a landmark for the plasma membrane. PIP2 promotes binding by allosterically triggering a conformational change in MA that exposes the myristyl group (4).

1. Massiah, M., Starich, M. R., Paschall, C. M., Summers, M. F., Christensen, A. M., Sunduist, W. I., "Three Dimensional Structure of the Human Immunodeficiency Virus Type-1 Matrix Protein." *J. Mol. Biol.* **244**, 198-223 (1994).

2. Christensen, A. M., Massiah, M. A., Turner, B. G., Sundquist, W. I., Summers, M. F. "Structure of the HTLV-II Matrix Protein and Comparison of Matrix Protein Structures from the Two Classes of Pathogenic Human Retroviruses," *J. Mol. Biol*. **264**, 1117-1131 (1996).

3. Tang, C., Loeliger, E., Luncsford, P., Kinde, I., Beckett, D., Summers, M. F., "Entropic switch regulates myristate exposure in the HIV-1 Matrix protein," *Proc. Natl. Acad. Sci. U.S.A.* **101**, 517-522 (2004).

4. Saad, J. S., Miller, J., Tai, J., Kim, A., Ghanam, R. H., Summers, M. F. "Structural basis for targeting HIV-1 Gag proteins to the plasma membrane for virus assembly," *Proc. Natl. Acad. Sci. U.S.A*., **103**, 11364-11369 (2006).

3. Structure, function, and antiviral targeting of retroviral Capsid and Gag proteins

An NMR-detected limited proteolysis method was used to show that the HIV-1 capsid (CA) protein contains a structurally distinct N-terminal domain (CA^{NTD}) (1). The structure of CA^{NTD} unexpectedly revealed that the protein exists primarily of □-helical elements arranged in a flat, triangular shape. The N-terminal NH2+ group forms a salt bridge with a strictly conserved and buried Asp side chain, stabilizing a □-hairpin motif. CA proteins from other retroviruses adopt similar overall structures (e.g., see (2)). The structure of the N-terminal half of HIV-1 Gag (MA through CA^{NTD}) revealed that residues of the N-terminal □-hairpin of the mature protein are unstructured in the immature MA-CA^{NTD} protein (3). We identified a novel class of small molecule antivirals that inhibit capsid assembly by binding to CA^{NTD}, the first discovered anti-CA antivirals (4).

1. Gitti, R.K., Lee, B.M., Walker, J., Summers, M.F., Yoo, S., Sundquist, W.I. "Structure of the Amino-Terminal Core Domain of the HIV-1 Capsid Protein," *Science* **273**, 231-235 (1996).

2. Khorasanizadeh, S., Campos-Olivas, R., Summers, M. F. “Solution Structure of the Capsid Protein from the Human T-Cell Leukemia Virus Type-I,” *J. Mol. Biol*. **291**, 491-505 (1999).

3. Tang, C., Ndassa, Y., Summers, M. F., “Structure of the N-terminal 283-residue fragment of the immature HIV-1 Gag polyprotein,” *Nature Struct. Biol*. **9**, 537-543 (2002).

4. Tang, C., Loeliger, E., Kinde, I., Kyere, S., Mayo, K., Barklis, E., Sun, Y., Huang, M., Summers, M. F. “Antiviral inhibition of HIV-1 capsid assembly,” *J. Mol. Biol*. **327**, 1013-1020 (2003).

4. Structure and function for retroviral genomic RNA

We showed that genome packaging by the Moloney Murine Leukemia Virus is regulated by a dimerization-dependent RNA structural switch mechanism, in which residues essential for genome packaging are sequestered by base pairing in the monomeric RNA and become exposed to promote retroviral NC binding upon dimerization (1). A hybrid NMR/cryo-EM method was used to solve the structure of a key MLV RNA packaging element (2). We developed a novel NMR method that enabled structural probing of the intact HIV-1 leader (> 700 nucleotide dimer), and showed that the leader undergoes dimerization-dependent remodeling that sequesters early-activity RNA signals (used for splicing and translation) exposes NC binding sites (3). We also identified a minimal region of the HIV-1 leader sufficient to direct RNA packaging, and determined it’s structure using a ^{2}H-edited NMR method we developed (4).

1. D'Souza, V. D., Summers, M. F., "Structural Basis for Packaging the Dimeric Genome of Moloney Murine Leukemia Virus," *Nature* **431**, 586-590 (2004).

2. Lu, K., Heng, X., Garyu, L., Monti, S., Garcia, E. L., Kharytonchyk, S., Dorjsuren, B., Kulandaivel, G., Jones, S., Hiremath, A., Sachin Divakaruni, S., LaCotti, C., Barton, S., Tummillo, D., Hosic, A., Edme, K., Albrecht, S., Telesnitsky, A., Summers, M. F., “NMR detection of structures in the HIV-1 5´-Leader RNA that regulate genome packaging,” *Science* 334, 242-245 (2011) 4.

3. Keane, S. C., Heng, X., Lu, K., Kharytonchyk, S., Ramakrishnan, V., Carter, G., Barton, S., Hosic, A., Florwick, A., Santos, J., Bolden, N. C., McCowin, S., Case, D. A., Johnson, B., Salemi, M., Telesnitsky, A., Summers, M. F. “Structure of the HIV-1 RNA packaging signal,” *Science* 348, 917-921 (2015).

4. Brown, J. D., Kharytonchyk, S., Chaudry, I., Iyer, A. S., Carter, H., Becker, G., Desai, Y., Glang, L., Choi, S. H., Singh, K., Lopresti, M. W., Orellana, M., Rodriguez, T., Oboh, U., Hijji, J., Ghinger, F. G., Stewart, K., Francis, D., Edwards, B., Chen, P., Case, D. A., Telesnitsky, A., Summers, M. F., “Structural Basis for Transcriptional Start Site Control of HIV-1 RNA Fate,” *Science* **386**, 413-417 (2020).

5. Ding, P., Kharytonchyk, S., Waller, A., Mbaekwe, U., Basappa, S., Kuo, N., Frank, H. M., Quasney, C., Kidane, A., Swanson, C., Van, V., Sarkar, M., Cannistraci, E., Chaudhary, R., Flores, H., Telesnitsky, A., Summers, M. F., “Identification of the initial nucleocapsid recognition element in the HIV-1 RNA packaging signal,” *Proc. Natl. Acad. Sci. U.S.A*, **117**, 17737-17746 (2020).

5. Structure and function of metalloproteins and enzymes

We used NMR methods to determine the first 3D structures of several zinc finger-like motifs, including LIM, TFIIB, and multiple types of retroviral zinc fingers (e.g., refs. 1,2). We used zinc substitution to determine the structure of a highly stable rubredoxin (Tm > 100 °C) from the hyperthermophile, Pyrococcus furiosus, and ^{113}Cd substitution to show that scalar couplings can be measured across NH—S hydrogen bonds (3). We determined the 3D structure of ketosteroid isomerase (which eluded X-ray structural characterization for more than 25 years), which established the structural basis for its ultra-fast catalytic activity (4).

1. Perez-Alvarado, G. C., Miles, C., Michelsen, J. W., Louis, H. A., Winge, D. R., Beckerle, M. C., Summers, M. F., “Structure of the Carboxy-terminal LIM domain from the cysteine rich protein CRP,” *Nature Structural Biology* **1**, 388-398 (1994).

2. Zhu, W., Zeng, Q., Colangelo, C. M., Michelle Lewis, L., Summers, M. F., Scott, R. A. “The N-Terminal Domain of TFIIB from Pyrococcus furiosus forms a Zinc Ribbon,” *Nature Structural Biology* **3**, 122-124 (1996)

3. Blake, P.R., Park, J.B., Adams, M.W.W., Summers, M.F. "Novel Observation of NH--S(Cys) Hydrogen Bond-Mediated Scalar Coupling in ^{113}Cd-Substituted Rubredoxin from Pyrococcus furiosus," *J. Am. Chem. Soc*. **114**, 4931 (1992)

4. Wu, Z. R., Ebrahimian, S., Zawrotny, M. E., Thornburg, L. D., Perez-Alvarado, G. C., Brothers, P., Pollack, R. M., Summers, M. F. "Solution Structure of 3-Oxo-Δ^5-Steroid Isomerase," *Science* **276**, 415-418 (1997).

Complete List of Published Work

Google Scholar: https://scholar.google.com/citations?user=uSS1Z90AAAAJ