BIOGRAPHICAL SKETCH

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NAME: Howard S. YOUNG

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

POSITION TITLE: Professor of Biochemistry, Faculty of Medicine & Dentistry

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
Trinity College, Hartford, CT USA	BSc	04/1987	Biochemistry
University of Connecticut, Farmington, CT, USA	PhD	12/1994	Biochemistry
New York University, New York, NY USA	PDF	1995-2001	Cell Biology & Biophysics

NOTE: The Biographical Sketch may not exceed five pages. Follow instructions below.

A. Personal Statement

Research Focus – Calcium is an essential signal carrier that enables cellular processes such as muscle contraction, secretion and metabolism. Consequently, calcium dysregulation is associated with many human diseases including heart failure, cancer, diabetes, Alzheimer's disease. Considering heart failure alone, 26 million people currently suffer worldwide. The principal site for cellular calcium homeostasis is the endo-sarcoplasmic reticulum (ER & SR), where a resident calcium pump (SERCA) actively maintains cytosolic calcium levels. SERCA is so important for cellular function that it is controlled by a number of tissue-specific master regulators – phospholamban (PLN), sarcolipin (SLN), myoregulin (MLN), Dworf, engoregulin (ELN) and another-regulin (ALN). Together, these SERCA regulators control vital life processes such as cardiac contractility (PLN & Dworf), atrial contractility and thermogenesis (PLN & SLN), and skeletal muscle performance (MLN & SLN). My research targets the role of these SERCA regulatory pathways in human disease. We use state-of-the-art biochemistry and structural biology to investigate the molecular mechanisms. As a unique aspect of our research, the structure-function studies are guided by human genetic variations in our target proteins. With this approach, we have made seminal contributions in our understanding of disease mechanisms associated with the dysregulation of cellular calcium homeostasis.

Expertise – The treatment of human disease requires detailed knowledge of disease-causing mechanisms. My expertise in biochemistry and structural biology can uniquely provide the necessary insights into the molecular pathology associated with membrane transport systems. We combine membrane reconstitution and mechanistic insights with molecular structure determination by X-ray crystallography, electron cryo-microscopy, and NMR spectroscopy. As genome sequencing rapidly expands the spectrum of known human mutations, one focus of our research is clinically relevant mutations in our target proteins (e.g. PLN & heart failure). This has enabled our research program to evolve toward the molecular basis for human disease. To the best of my knowledge, we are one of the few labs in the world specializing in this skill set – patient-directed research, human mutations, membrane reconstitution, and structural biology – to understand human molecular pathology.

Commitment – My research program in membrane biology is recognized as a priority area by the University of Alberta, and it is situated within one of the top Biochemistry departments in North America. The commitment to research in Alberta is exceptional, with contributions at the provincial, institutional, faculty and departmental levels. I have received numerous salary, equipment and trainee awards from Alberta Innovates Health Solutions. The complete support environment is too extensive to describe herein. Notably, it includes laboratory space, key

infrastructure and equipment, conference facilities, subsidized core facilities, clinical facilities, research funding opportunities, funding for visiting speakers and conferences, and numerous trainee awards.

B. Positions and Honors

1995-2001 Postdoctoral Fellow, Laboratory of Dr. David L. Stokes, Skirball Institute, New York University School of Medicine, New York, N.Y.

2001-2002 Instructor, Laboratory of Dr. David L. Stokes, Skirball Institute, New York University School of Medicine, New York, N.Y.

2002-2007 Assistant Professor, Department of Biochemistry, University of Alberta, Edmonton, AB, Canada

2007-2012 Associate Professor, Department of Biochemistry, University of Alberta, Edmonton, AB, Canada

2008-present Cross-Appointed, National Institute for Nanotechnology, University of Alberta, Edmonton, AB

2012-present Professor, Department of Biochemistry, University of Alberta, Edmonton, AB, Canada

Other Experience and Professional Memberships

1992-present Biophysical Society

2004-2005 Organizing committee – 14th International Symposium on Calcium and Calcium Binding Proteins in Health and Disease, April 5-10, 2005. Banff, Alberta, Canada.

2005-present Faculty Recruitment Committee – Department of Biochemistry, University of Alberta

2006-2007 Organizing committee – 34th Annual Meeting of the Microscopical Society of Canada, June 12-15, 2007. University of Alberta, Lister Conference Center, Edmonton, Alberta, Canada.

2007-2011 Biochemistry A peer review panel, Canadian Institutes of Health Research

2007 AHFMR Graduate Studentship Awards Committee

2007-2009 Advisory Committee to the Chair, Biochemistry, University of Alberta

2008-2010 Organizing committee – Annual Meeting of the Canadian Society of Molecular Biosciences – Membrane Proteins in Health and Disease, April 15-18, 2010. Banff Center, Banff, Alberta, Canada.

2009-2012 Elected member, Faculty Evaluation Committee, Faculty of Medicine and Dentistry, University of Alberta

2012-2014 Co-Chair – Annual Meeting of the Canadian Society of Molecular Biosciences – Membrane Proteins in Health and Disease, April 10-13, 2014. Banff Center, Banff, Alberta, Canada.

2014-2018 Chair – Annual Meeting of the Canadian Society of Molecular Biosciences – Membrane Proteins in Health and Disease, April 15-18, 2018. Banff Center, Banff, Alberta, Canada.

2017-2022 Chair – Organizing Committee, P-Type ATPases in Heath and Disease, 16th International Conference on Na,K-ATPase and Related Transport ATPases. September 1-6, 2022. Banff Center, Banff, Alberta, Canada (this conference has been delayed due to the pandemic).

Honors

2007-2014 Alberta Innovates Health Solutions, Senior Scholar

2002-2007 Canadian Institutes of Health Research, New Investigator

2002-2007 Alberta Heritage Foundation for Medical Research, Scholar

1999-2002 American Heart Association, Scientist Development Award

1996-1998 National Research Service Award Postdoctoral Fellowship, National Institutes of Health, National Institute of General Medical Sciences.

C. Contribution to Science (trainees are underlined)

Molecular Insights into Heart Failure

We have provided important insights into the impaired calcium homeostasis associated with heart failure. Here are examples of the novelty and impact of our research. A mutation in phospholamban (Arg^{9}-Cys) causes

lethal dilated cardiomyopathy (DCM). To understand how it causes disease, we undertook extensive structure-function studies. We discovered that the hydrophobic change introduced by the Arg^9-Cys mutation disrupted phospholamban function and sarcoplasmic reticulum (SR) calcium homeostasis (Ceholski et al., 2012ab; Young et al., 2015) and that an Arg^9-Leu mutation completely mimicked this behavior. This led us to predict that the Arg^9-Leu mutation would be found in DCM patients, which was confirmed in two Brazilian patients (our findings were featured on Global TV & CTV News). Importantly, this was our motivation for gene sequencing of heart failure patients and the development of prognostic models for disease-causing mutations.

Toward our goal of rational drug design to treat heart failure, we have provided novel structural insights into SR calcium transport proteins critical for cardiac contractility. Our state-of-the-art techniques include X-ray crystallography (Moncoq et al., 2007; Laursen et al., 2009), cryo-EM (Stokes et al., 2006; Glaves et al., 2011, 2019, & 2020), and NMR spectroscopy (Andronesi et al., 2005; Seidel et al., 2008).

1. Glaves, J.P.*, Primeau, J.O.*, Espinoza-Fonseca, L.M., Lemieux, M.J., **Young, H.S.** (2019) The phospholamban pentamer interacts with the sarcoplasmic reticulum calcium pump SERCA. *Biophysical Journal* 116:633-47.
2. Ceholski, D.K., Trieber, C.A., **Young, H.S.** (2012) Hydrophobic imbalance in the cytoplasmic domain of phospholamban is a determinant for lethal dilated cardiomyopathy. *Journal of Biological Chemistry* 287:16521-9.
3. Glaves, J.P., Trieber, C.A., Ceholski, D.K., Stokes, D.L., **Young, H.S.** (2011) Phosphorylation and mutation of phospholamban alter physical interactions with the sarcoplasmic reticulum calcium pump. *Journal of Molecular Biology* 405:707-23.
4. Seidel, K., Andronesi, O.C., Krebs, J., Griesinger, C., **Young, H.S.**, Becker, S., and Baldus, M. (2008) Structural characterization of Ca^{2+}-ATPase-bound phospholamban in lipid bilayers by solid-state NMR spectroscopy. *Biochemistry* 47:4369-76.

Productivity

My lab has an excellent record of productivity. Over the last 7 years, I have contributed 22 peer reviewed publications (63 publications over my career) in journals such as *Journal of Biological Chemistry* (13 papers), *PLoS Pathogens* (1), *Biochemistry* (5), *Biophysical Journal* (5), *FEBS Journal* (2), *Journal of Molecular Biology* (1), *Journal of the American Chemical Society* (1), *The Plant Journal* (1), *Biochemistry and Cell Biology* (1), *PLoS One* (1), *RNA Biology* (1), amongst others. I have also contributed 8 structures to the Protein Data Bank (5 of the sarcoplasmic reticulum calcium pump SERCA and 3 drug complexes of the SARS-CoV-2 main protease). We are the only lab in Canada to have solved structures of this family of proteins by X-ray crystallography.

1. Glaves, J.P., Primeau, J.O., Espinoza-Fonseca, L.M., Lemieux, M.J., **Young, H.S.** (2020) Interaction of a sarcolipin monomer and pentamer with the sarcoplasmic reticulum calcium pump SERCA. *Biophysical Journal* 118:518-31.
2. Smeazzetto, S.*, Armanious, G.A.*, Moncelli, M.R., Bak, J.J., Lemieux, M.J., **Young, H.S.#**, Tadini-Buonunsegni, F.# (2017) Conformational memory in the association of the transmembrane protein phospholamban with the sarcoplasmic reticulum calcium pump SERCA. *Journal of Biological Chemistry* 292:21330-9.
3. Gorski, P.A., Trieber, C.A., Ashrafi, G., **Young, H.S.** (2015) Regulation of the sarcoplasmic reticulum calcium pump by divergent phospholamban isoforms in zebrafish. *Journal of Biological Chemistry* 290:6777-88.
4. Laursen M., Bublitz M., Moncoq K., Olesen C., Moeller J.V., **Young H.S.**, Nissen P., Morth J.P. (2009) Cyclopiazonic acid is complexed to a divalent metal ion when bound to the sarcoplasmic reticulum Ca^{2+}-ATPase. *Journal of Biological Chemistry* 284: 13513-8.

Impacting Health Outcomes

We are characterizing the dysregulation of SERCA-dependent calcium homeostasis in hearts, with an emphasis on proteolytic cleavage or human missense variants in calcium regulatory proteins and their linkage to heart failure. We have published an early prognostic model based on mutations in the calcium transport regulatory protein PLN (Young et al., 2015). As an example of the use of our prognostic models, I consulted on a 11 year old patient with intellectual disability and seizures. Gene sequencing unexpectedly identified a heterozygous deletion of the PLN gene (previously unknown). Our comparison to known mutations revealed that the patient will likely develop hypertrophy with relatively normal contractility, rather than the more severe DCM.I also consuted on a family in Lethbrdige, Alberta, Canada who harbor the Arg14-deletion mutation commonly found in the Netherlands (the family immigrated to Canada). Two family members have severe DCM and two

family members are asymptomatic carriers. We have advised their clinical team on the relationship between demand for cardiac output and the development of DCM. This information facilitated a more effective treatment plan for these patients.

1. Roczkowsky A., Chan B.Y.H., Lee T.Y.T., Mahmud Z., Hartley B., Julien O., Armanious G., **Young H.S.**, Schulz R. (2019) Myocardial MMP-2 contributes to SERCA2a proteolysis during cardiac ischemia-reperfusion injury. *Cardiovascular Research* 116:1021-31.
2. **Young, H.S.**, Ceholski, D.K., Trieber, C.A. (2015) Deception in simplicity: Hereditary phospholamban mutations in dilated cardiomyopathy. *Biochemistry and Cell Biology* 93:1-7.
3. Abrol, N., Smolin, N., Armanious, G., Ceholski, D.K., Trieber, C.A., **Young, H.S.**, Robia, S.L. (2014) Phospholamban C-terminal residues are critical determinants of the structure and function of the calcium ATPase regulatory complex. *Journal of Biological Chemistry* 289:25855-66.
4. Ceholski, D.K., Trieber, C.A., Holmes, C.F., **Young, H.S.** (2012) Lethal, hereditary mutants of phospholamban elude phosphorylation by protein kinase A. *Journal of Biological Chemistry* 287:26596-605.

Mechanistic Insights into SERCA Regulation

Over the last 18 years, we have made important discoveries in the area of SERCA regulation. During this past year and the Covid-19 pandemic, we have used our expertise in X-ray crystallography to solve 14 structures of the SARS-CoV-2 main protease in complex with antiviral drugs (PDB codes 6WTK, 6WTM, & 6WTJ; 8 additional structures deposited and awaiting release). These structure were determined in my laboratory, though they are part of an antiviral research team.

1. Vuong, W., Khan, M.B., Fishcer, C., Arutyunova, E., Lamer, T., Shields, J., Bandi, H., McKay, R.T., van Belkum, M., Joyce, M., **Young, H.S.**, Tyrrell, D.L., Vederas, J.C., Lemieux, M.J. (2020) Feline coronavirus drug inhibits the main protease of SARS-CoV-2 and blocks virus replication. *Nature Communications* (Aug 27) 11:4282.
2. Gorski, P.A., Trieber, C.A., Ashrafi, G., **Young, H.S.** (2015) Regulation of the sarcoplasmic reticulum calcium pump by divergent phospholamban isoforms in zebrafish. *Journal of Biological Chemistry* 290:6777-88.
3. Gorski, P.A., Trieber, C.A., Larivière, E., Schuermans, M., Wuytack, F., **Young, H.S.**, Vangheluwe, P. (2012) Transmembrane helix 11 is a genuine regulator of the endoplasmic reticulum Ca2+ pump and acts as a functional parallel of β-subunit on α-Na+,K+-ATPase. *Journal of Biological Chemistry* 287:19876-85. **I am a corresponding author and the first two authors are my trainees.*
4. Gorski, P.A., Glaves, J.P., Vangheluwe, P., **Young, H.S.** (2013) Sarco/endoplasmic reticulum calcium ATPase (SERCA) inhibition by sarcolipin is encoded in its luminal tail. *Journal of Biological Chemistry* 288:8456-67.

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

Ongoing Research Support

National Institutes of Health
R01HL092321
"Regulation of cardiac calcium transport"
02/2018-01/2022
My goal for this project is to obtain structures of SERCA-phospholamban regulatory complexes by cryo-electron microscopy.
Role: Subcontract

National Institutes of Health
R01HL143816
"New mechanisms of SERCA regulation: Dimerization and micropeptides"
01/2019-11/2022
My goal for this project is to obtain structures of SERCA-micropeptide regulatory complexes by cryo-electron microscopy.
Role: Subcontract

Heart and Stroke Foundation of Canada
“Mechanisms of SERCA activation and inhibition in dilated cardiomyopathy.”
Howard Young (PI)
06/2019-05/2022
The goals of this project are to explore the molecular genetics of SERCA dysregulation in heart failure.
Role: PI

Completed Research Support

Alberta Prion Research Institute & Alberta Alzheimer’s Research Program
“Atomic resolution structures of β amyloid intermediates”
04/2017-03/2019
The goals of this project are to explore the molecular structures of amyloid intermediates in Alzheimer’s disease.
Role: PI

National Science and Engineering Research Council
“Joint Alberta-Germany International Research Group in Membrane Biology”
06/2012-07/2018
This is a group training program in membrane biology, which includes the University of Alberta (Alberta, Canada), and the University of Kaiserslautern and Saarland University (Germany).
Role: Co-PI

Heart and Stroke Foundation of Canada
“Mechanisms of SERCA dysregulation in dilated cardiomyopathy.”
Howard Young (PI)
06/2016-05/2019
The goals of this project are to explore the molecular genetics of SERCA dysregulation in heart failure.
Role: PI

Canadian Institutes for Health Research
“Membrane transport and ion homeostasis in cardiac muscle.”
Howard Young (PI)
03/2010-04/2017
The goals of this project are to explore the molecular mechanisms of SERCA calcium pump regulation.
Role: PI

Heart and Stroke Foundation of Canada
“Mechanistic insights into SERCA dysregulation in dilated cardiomyopathy.”
Howard Young (PI)
06/2012-05/2015
Role: PI