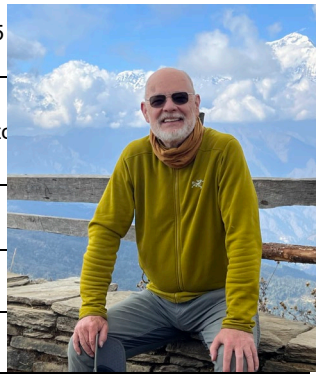
OMB No. 0925-0001 and 0925-0002 (Rev. 10/15



BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributo
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Zygmunt S. Derewenda

eRA COMMONS USER NAME (credential, e.g., agency login): ZSD4NNIH

POSITION TITLE: Professor of Molecular Physiology and Biological Physics

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 Lodz, Poland	M.Sc.	1997	Biochemistry Chemistry
University of Lodz, Poland	Ph.D.	1982	Crystallography
University of York, United Kingdom	Postdoctoral	1985-1990	Protein Crystallography

A. Personal Statement

I had the great fortune and privilege to begin my professional career working with the early pioneers of macromolecular crystallography, Max Perutz and Dorothy Hodgkin. I was naturally influenced by their fascination with protein structure and function as explore by X-ray diffraction methods, but even more so their inviolate standards of ethics in science which they adhered to, and their dedication to science as a collaborative activity. My priority has always been to focus on important problems in structural biology, and to do so with the help of expert collaborators. Since I took up an independent position at the University of Alberta in Edmonton, I vastly expanded the experimental methodology in the lab to include a broad range of molecular biology and biochemistry tools, such as expression of proteins in both prokaryotic and eukaryotic cells, and a range of biophysical methods. Most of my papers feature interdisciplinary studies and are collaborative. My contributions to science include more than 110 depositions to the PDB, and more than 170 papers and book chapters which, according to the Google Scholar database that track all publications, collectively have attracted over 17,000 citations (h-index 65).

In 1996, I was recruited by the University of Virginia to the Department of Molecular Physiology and Biological Physics, by the late Dr. Andrew Somlyo, a renowned smooth muscle physiologist. Together with Dr. Avril Somlyo we embarked on a collaborative project aimed at the elucidation of select signaling pathways in smooth muscle, and our funding has been in place with short breaks for over 20 years. We have recently made considerable progress focusing on the structure and function of the RSK2 kinase in the vascular system. Our laboratory has contributed specifically to the understanding of structure-function relationships and inhibitor binding. We were excited to discover with Dr. Avril Somlyo that RSK2 is a physiologically active kinase in smooth muscle and that is plays an important role in the regulation of contractility. I have been intimately involved in this project for the last few years and worked together with Dr. A Somlyo planning experiments and interpreting the data.

B. Positions and Honors

Positions and Employment

1982-1985	Department of Crystallography University of Lodz, Poland	Assistant Professor
1985-1988	Department of Chemistry, University of York, U.K.	Research Fellow
1988-1990	Department of Chemistry, University of York, U.K.	Research Associate
1991-1995	University of Alberta, Edmonton, Canada	Associate Professor
1996-present	Department of Mol. Physiology & Biophysics, UVA, USA	Professor

Other Experience and Professional Memberships

Scientific Consultant for Procter & Gamble Co.		1994
Scientific Consultant for NIDO Biosciences		2022-2023
Member of:	American Crystallographic Association	
	American Society for Biochemistry and Molecular Biology	
	American Chemical Society	
	American Association for the Advancement of Science	

Academic Service, Professional Honors and awards (selected, since 2000 only)

NIH Study Sections (various, ad hoc, member and Chair)	2001-2022
DSc (*Doctor habilitatus*) University of Lodz, Poland	2004
DOD Review Panels	2004-2008
NIH PSI Integrated Center for Structure-Function Innovation, Co-Director	2005-2010
Co-Editor of Acta Crystallographica Section D (Biological Crystallography)	2010-present
Medal *Universitatis Lodziensis Amico* (bestowed by the Senate of the University of Lodz)	2011
Foundation for Polish Science, Annual Prize Nominating Committee Member	2014-2017
David A. Harrison Distinguished Teaching Professor, University of Virginia	2014-2019, 2021-present
David A. Harrison Distinguished Educator Award	2017
MSFC NIH Study Section Permanent Member	2016-2022
Foreign Member, Faculty Council, Faculty of Biology and Environmental Protection University of Lodz, Poland	2018-2021

C. Contributions to Science (> 170 publications; 1 patent, h=65, total citations 17,789)

I have contributed in a meaningful way to several fields of structural biology, as illustrated by citations. I am listing chronologically those that I consider most important, with representative publications and their impact (numbers of citations, from the Google Scholar database, as of October 2022.

1. Most current: Studies of the signaling pathways in smooth muscle

After moving to the University of Virginia, I established a close collaboration with Drs. Andrew and Avril Somlyo, who were renowned for their pioneering studies of smooth muscle physiology and in particular Ca^{2+}-sesitization of SM contraction. While, sadly, Dr. Andrew Somlyo passed away in 2004, our collaboration with Dr Avril Sonlyo continues to date, and we have been almost continuously funded until present (our grant will support us until 2018). Our research focuses on the understanding of the structure and function of protein involved in the signaling cascades that modulate Ca^{2+}-sensitivity. My work has been as a co-leader of this project, intellectually involved in all aspects, but technically involved in the crystallographic and biophysical characterization of proteins and their complexes. We have been the first group to provide structural characterization of RhoA and to visualize how it binds to its regulator RhoGDI, we discovered how PDZRhoGEF is involved in Ca^{2+}-sensitization, and made a number of important discoveries.

Wei Y, Zhang Y, Derewenda U, Liu X, Minor W, Nakamoto RK, Somlyo AV, Somlyo AP, **Derewenda ZS**. Crystal structure of RhoA-GDP and its functional implications. Nat Struct Biol. 1997 Sep;4(9):699-703. **Citations: 241**

Longenecker K, Read P, Derewenda U, Dauter Z, Liu X, Garrard S, Walker L, Somlyo AV, Nakamoto RK, Somlyo AP, **Derewenda ZS**. How RhoGDI binds Rho. Acta Crystallogr D Biol Crystallogr. 1999 Sep;55(Pt 9):1503-15. **Citations: 115**

Derewenda U, Oleksy A, Stevenson AS, Korczynska J, Dauter Z, Somlyo AP, Otlewski J, Somlyo AV, **Derewenda ZS**. The crystal structure of RhoA in complex with the DH/PH fragment of PDZRhoGEF, an activator of the Ca(2+) sensitization pathway in smooth muscle. Structure. 2004 Nov;12(11):1955-65. **Citations: 112**

Momotani K, Artamonov MV, Utepbergenov D, Derewenda U, **Derewenda ZS**, Somlyo AV. p63RhoGEF couples Gα(q/11)-mediated signaling to Ca^{2+} sensitization of vascular smooth muscle contractility. Circ Res. 2011 Oct 14;109(9):993-1002. PMC3211138 **Citations: 92**

Artamonov MV, Sonkusare SK, Good ME, Momotani K, Eto M, Isakson BE, Le TH, Cope EL, **Derewenda ZS**, Derewenda U, Somlyo AV RSK2 contributes to myogenic vasoconstriction of resistance arteries by activating smooth muscle myosin and the Na^+/H^+ exchanger. Sci Signal. 2018 Oct 30;11(554). PMID: 30377223
Citations 9

2. Establishing the precise molecular mechanism of oxygenation in haemoglobin
I initiated this project with friends, when we were graduate students. We observed that human haemoglobin can be crystallized in a deoxy form from polyethylene glycol, and then oxygenated on the β-chain only, or even on all chains, while retaining the T quaternary structure. This work resulted in several high-profile papers (note alphabetical order of names, normally I would be the first author) and a major revision of the theory of cooperative oxygenation of haemoglobin. Although this was my first project, I had conceived the work from the start, and was intimately involved in most stages, until the project was taken further by the Dodson lab in York and I moved on to other work.

Brzozowski A, **Derewenda Z**, Dodson E, Dodson G, Grabowski M, Liddington R, Skarzyński T, Vallely D. Bonding of molecular oxygen to T state human haemoglobin. Nature. 1984 307 (5946):74-6. **Citations: 127**

Liddington R, **Derewenda Z**, Dodson G, Harris D. Structure of the liganded T state of haemoglobin identifies the origin of cooperative oxygen binding. Nature. 1988 331 (6158):725-8. **Citations: 120**

Liddington, R, Derewenda, Z.S., Dodson, E.J., Hubbard, R., Dodson, G.G. High resolution crystal structures and comparisons of T-state deoxyhaemoglobin and two liganded T-state haemoglobins: T (α-oxy) haemoglobin and T (met) haemoglobin. J. Mol. Biol. 1992, 228:551-579. **Citations: 119**

3. Studies of structure-function relationships in human insulin
This was one of the main projects I was in charge of as a Senior Research Fellow in York. My position was funded by NOVO-Nordisk, at the time a leading insulin manufacturer and our work focused on improving insulin preparations, including protein engineering which was a pioneering feat in the 80s. Several of the hormones we studied were later approved for use and the work was confidential. Our groundbreaking study on the interaction of phenol with insulin allowed Novo to produce preserving agents with lower toxicity that are used to date in clinical preparations. I carried out much of the crystallography assisted also by Dr. Urszula Derewenda.

Derewenda U, **Derewenda Z**, Dodson EJ, Dodson GG, Reynolds CD, Smith GD, Sparks C, Swenson D. Phenol stabilizes more helix in a new symmetrical zinc insulin hexamer. Nature. 1989 Apr 13;338(6216):594-6. **Citations: 411**

Derewenda U, **Derewenda** Z, Dodson EJ, Dodson GG, Bing X, Markussen J. X-ray analysis of the single chain B29-A1 peptide-linked **insulin** molecule. A completely inactive analogue. J Mol Biol. 1991 Jul 20;220(2):425-33. **Citations: 225**

4. Structure and function of hydrolytic enzymes.
Another high-impact project that I was put in charge of was the investigation of a range of hydrolytic enzymes with potential for industrial use. This was initially also in collaboration with Novo-Nordisk in York, but later I continued to work in this area after I established my independent group in Edmonton, Canada. The papers that emerged from this area of investigation are among my most cited publications and include the explanation of the mechanism of enzymatic hydrolysis of neutral lipids and of the mechanism of interfacial activation in neutral lipases (while I was the first author, the papers were published with alphabetical order of names). I was also the author of the first study of a thioesterase and a platelet activating factor hydrolase. The enzymes we studied for Novo are still used on the market as additives to laundry detergent.

Brady L, Brzozowski AM, **Derewenda ZS**, Dodson E, Dodson G, Tolley S, Turkenburg JP, Christiansen L, Huge-Jensen B, Norskov L, et al. A serine protease triad forms the catalytic centre of a triacylglycerol lipase. Nature. 1990 Feb 22;343(6260):767-70. **Citations: 1572**

Brzozowski AM, Derewenda U, **Derewenda ZS**, Dodson GG, Lawson DM, Turkenburg JP, Bjorkling F, Huge-Jensen B, Patkar SA, Thim L. A model for interfacial activation in lipases from the structure of a fungal lipase-inhibitor complex. Nature. 1991 Jun 6;351(6326):491-4. **Citations: 1354**

Ho YS, Swenson L, Derewenda U, Serre L, Wei Y, Dauter Z, Hattori M, Adachi T, Aoki J, Arai H, Inoue K, **Derewenda ZS**. Brain acetylhydrolase that inactivates platelet-activating factor is a G-protein-like trimer. Nature. 1997 Jan 2;385 (6611):89-93. **Citations: 207**

5. Development of novel approaches to macromolecular crystallization.
Crystallography continues to be my passion. More than two decades ago, I became intrigued by the problem of macromolecular crystallization, which is – due to low rates of success and irreproducibility – a real bottleneck in structural biology. I conceived a method to engineer the target proteins by site directed mutagenesis, to make them more susceptible to crystallization using classical screening methods. This idea was based on a hypothesis that certain amino acids with large side chains. I went on to validate this experimentally and proposed a strategy of surface engineering that allows one to make variants of protein for crystallization. The method has also been adopted by Pharmaceutical companies, because it often allows generating new crystal forms of drug target, better suited for structural characterization. I have been funded by the NIH since 2000 until 2016 for this project, and, among others, we helped develop with Dr. David Eisenberg (UCLA) a popular server, which helps design crystallizable variants.

Longenecker KL, Garrard SM, Sheffield PJ, **Derewenda ZS**. Protein crystallization by rational mutagenesis of surface residues: Lys to Ala mutations promote crystallization of RhoGDI. Acta Crystallogr D Biol Crystallogr. 2001 May;57(Pt 5):679-88. Epub 2001 Apr 24. **Citations: 189**

Derewenda ZS. Rational protein crystallization by mutational surface engineering. Structure. 2004 Apr;12(4):529-35. **Citations: 386**

Derewenda ZS, Vekilov PG. Entropy and surface engineering in protein crystallization. Acta Crystallogr D Biol Crystallogr. 2006 Jan; 62(Pt 1):116-24. Epub 2005 Dec 14. Review. **Citations: 310**

Goldschmidt L, Cooper DR, **Derewenda ZS**, Eisenberg D. Toward rational protein crystallization: A Web server for the design of crystallizable protein variants.Protein Sci. 2007 Aug;16(8):1569-76. **Citations: 336**

My Bibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1lsknP6bTDN50/bibliography/48507602/public/?sort=date&direction=ascending

D. Current Research Support

R21 NS118647 (MPIs- Derewenda, Z.S., Somlyo, A.V., Sonkusare, S.) 06/01/2020 – 11/30/2023
NIH/NIGMS
Molecular Mechanisms of RhoA-mediated Ca^{2+} Sensitization in Vascular Smooth Muscle
Goals: The overarching aim of this proposal is to identify those signaling pathways in SM that are critical to the regulation of contractility via Ca^{2+}-sensitization and RhoA, and to elucidate at the cellular and structural level, how specific GEFs and GAPs function in these pathways.