

**BIOGRAPHICAL SKETCH**

NAME Arvan, Peter	POSITION TITLE Professor and Chief, Division of Metabolism, Endocrinology & Diabetes, University of Michigan		
eRA COMMONS USER NAME (credential, e.g., agency login) parvan			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Cornell Univ School of Arts and Sciences, New York	AB	1977	Biochemistry
Yale Univ School of Medicine (MSTP), Connecticut	MD	1984	Medicine
Yale Univ School of Medicine (MSTP), Connecticut	PhD	1984	Cell Biology

**A. Positions and Honors.****A. 1. Training and Professional Positions:**

1979-'84: Dissertation Research, Dept. of Cell Biology, Yale U. School of Med., New Haven, CT.  
 1984-'85: Intern in Medicine, North Carolina Memorial Hospital, Chapel Hill, NC.  
 1985-'88: Research-Residency Program, Yale University School of Medicine, New Haven, CT.  
 1985-'86 Endocrine research fellow with Dr. Howard Rasmussen, Yale U., New Haven CT.  
 1986-'87: Resident in Internal Medicine, Yale-New Haven Hospital, New Haven, CT.  
 1987-'88: Fellow in Endocrinology, Yale-New Haven Hospital, New Haven, CT.  
 1988-'95: Ass't Prof. of Med., Program in Biological and Biomedical Sciences, Harvard Med. School; and Division of Endocrinology; Beth Israel Hospital, Boston MA.  
 1996: Associate Professor, Program in Biological and Biomedical Sciences, Harvard Med. School; and Division of Endocrinology; Beth Israel Hospital, Boston MA.  
 1996-: Associate Professor of Medicine, Division of Endocrinology, AECOM, Bronx, NY.  
 1996-: Associate Professor, Dept. of Developmental and Molecular Biology, AECOM, Bronx, NY.  
 2000-'03: Professor of Medicine, Division of Endocrinology, AECOM, Bronx, NY.  
 2000-'03: Professor, Dept. of Developmental and Molecular Biology, AECOM, Bronx, NY.  
 2003-: Professor and Chief, Division of Metabolism, Endocrinology & Diabetes, University of Michigan Medical School, Ann Arbor, MI  
 2003-: Professor, Program in Cell and Molecular Biology, U. Mich. Med. School, Ann Arbor, MI  
 2005-'06 Interim Director, Michigan Comprehensive Diabetes Center, Univ. of Mich, Ann Arbor, MI  
 2006-pre Director, Michigan Comprehensive Diabetes Center, Univ. of Michigan, Ann Arbor, MI

**A. 2. Hospital Appointments:**

1988-'96 Beth Israel Hospital Boston, MA  
 1996-'03 Jacobi, Montefiore, and Einstein Hospitals, Bronx NY  
 2003-: University of Michigan, University Hospital, Ann Arbor MI

**A. 3. Awards, Honors, and Other Selected Professional Activities:**

1977: Phi Beta Kappa  
 1977-'84 Medical Scientist Training Program (NIH) at Yale U. School of Medicine  
 1988: PEW Scholar in the Biomedical Sciences: Secretory protein targeting  
 1995: American Society for Clinical Investigation, elected member  
 1997 Symposium Speaker: American Diabetes Assoc. Meeting, Boston MA  
 1998 Invited Speaker: European Science Foundation Meeting on Exocytic membrane Traffic, Giens, France  
 1998 Speaker, Division of Endocrinology, Vanderbilt U., Nashville TN  
 1999: Wellcome Visiting Professorship in the Basic Medical Sciences  
 1999-'03: Irma T. Hirschl Career Scientist Award  
 1999-'01: Invited Faculty, Molecular/Cellular Research Course, San Diego CA  
 2000: Monbusho Grant-in-Aid for International Scientific Research (Ministry of Education and Science of Japan)  
 2001 Speaker, Division of Endocrinology, Baylor College of Medicine, Houston TX  
 2001 Speaker, Division of Molecular Medicine, OHSU, Portland OR  
 2001 Invited Speaker, Novo/Nordisk, Bagsvaerd, Denmark

- 2001 Speaker, Dept. of Cell Biology, U. of Pittsburgh, Pittsburgh PA  
 2001: Symposium Speaker: Endocrine Society meeting, Denver, CO  
 2001: Session Chair, Molecular Membrane Biology Gordon Conference  
 2002 Invited Speaker, Dipartimento di Biologia e Patologia Cellulare e Molecolare, University Federico II School of Medicine, Naples, Italy  
 2003 Speaker, Dept. of Cell Biology, Cleveland Clinic, Cleveland OH  
 2003 Keystone Symposium Session Chair and Speaker: Pancreatic Islet Cell Biology, Keystone CO  
 2003 ASBMB Symposium Session Chair and Speaker: New Insights into  $\beta$ -cell biology. San Diego CA  
 2003 R.R. Bensley Award + Lecture (Am. Assoc. Anat., San Diego CA)  
 2003 Speaker, Dept. of Physiology/Biophysics, Boston U. School of Med., Boston MA  
 2003 Brehm Endowed Professorship in Diabetes, University of Michigan, Ann Arbor  
 2004 Session Chair, Metabolomics and Obesity Symposium, University of Michigan, November 4, 2004  
 2005-'08: **Regular member, NIH MCE (Molecular and Cellular Endocrinology) Study Section**  
 2005 Chair, Michigan Comprehensive Diabetes Center Operating Committee  
 2006 Mexico National Institute of Public Health (INSP) Recognition Award for best publication of 2005 (Ramos-Castañeda J, et al. J. Biol. Chem. 280: 9467)  
 2006 Symposium Speaker, International Congress of Biochem./Molec. Biol., Kyoto, Japan  
 2006 Symposium Speaker, Mechanisms of Hormone Secretion. Endo Society mtg. Boston, MA  
 2007 Michigan Diabetes Research and Training Center Executive Committee  
 2007 Association of American Physicians (**AAP**), **elected member**  
 2007 Symposium Speaker, American Diabetes Association "Translating Islet Biology into Diabetes Therapy", Stone Mountain GA  
 2007- Organizer and participant, Brehm Coalition for Discovery in Type 1 Diabetes  
 2008 NIH intramural BSC Ad hoc reviewer panel

**A. 4. Editorial Boards and Relevant Society-related Activities:**

- 1994, 1995, 1997, 2001, 2002 Special reviewer Endocrinology Study Section NIH  
 1998-2000 The Journal of Biological Chemistry  
 2000 Grant Reviewer, American Thyroid Association  
 2001-2005 American Journal of Physiology: Endocrinology and Metabolism  
 2005-2008 Regular member NIH MCE Study Section  
 1998-present Thyroid  
 2008-2009 Associate Editor: American Journal of Pathology

**B. Selected peer-reviewed publications (in chronological order).**

- Arvan P, Lee J. Regulated and constitutive protein targeting can be distinguished by secretory polarity in thyroid epithelial cells. J. Cell Biol. 1991; 112:365-376.
- Arvan P, Kuliawat R, Prabakaran D, Zavacki A-M, Elahi D, Wang S, Pilkey D. Protein discharge from immature secretory granules displays both regulated and constitutive characteristics. J. Biol. Chem. 1991; 266:14171-14174.
- Kuliawat R, Arvan P. Protein targeting via the "constitutive-like" secretory pathway in isolated pancreatic islets: passive sorting in the immature granule compartment. J. Cell Biol. 1992; 118:521-529.
- Arvan P, Castle JD. Protein sorting and secretion granule formation in regulated secretory cells. Trends in Cell Biol. 1992; 2:327-331.
- Huang X-F, Arvan P. Formation of the insulin-containing secretory granule core occurs within immature  $\beta$ -granules. J. Biol. Chem. 1994; 269:20838-20844.
- Kuliawat R, Arvan P. Distinct molecular mechanisms for protein sorting within immature secretory granules of pancreatic  $\beta$ -cells. J. Cell Biol. 1994; 126:77-86.
- Huang X-F, Arvan P. Intracellular transport of proinsulin in pancreatic  $\beta$ -cells: structural maturation probed by disulfide accessibility. J. Biol. Chem. 1995; 270:20417-20423.
- Kuliawat R, Klumperman J, Ludwig T, Arvan P. Differential sorting of lysosomal enzymes out of the regulated secretory pathway in pancreatic B-cells. J. Cell Biol. 1997; 137:595-608.
- Klumperman J, Kuliawat R, Griffiths JM, Geuze HJ., Arvan P. Mannose 6-phosphate receptors are sorted from immature secretory granules via AP- 1, clathrin, and syntaxin 6-positive vesicles. J. Cell Biol. 1998; 141:359-371.
- Arvan P, Castle JD. Sorting and storage during secretory granule biogenesis: looking backward and looking forward. Biochemical Journal. 1998; 332:593-610.

11. Gorr S-U, Huang XF, Cowley DJ, Kuliawat R, Arvan P. Disruption of disulfide bonds exhibits differential effects on the trafficking of regulated secretory proteins. *Am. J. Physiol.: Cell Physiol.* 1999; 277:C121-C132.
12. Shields, D, Arvan P. Disease models provide insights into post-Golgi protein trafficking, localization, and processing. *Curr. Opin. Cell Biol.* 1999; 11:489-494.
13. Kuliawat R, Arvan P. Storage granules of the regulated secretory pathway: structure and function. *The Einstein Quarterly Journal.* 1999; 16:29-40.
14. Turner M, Arvan P. Protein traffic from the secretory pathway to the endosomal system in pancreatic  $\beta$  cells. *J. Biol. Chem.* 2000; 275:14025-14030.
15. Tokunaga F, Brostrom C, Koide T, Arvan P. ER-associated degradation of misfolded N-linked glycoproteins is suppressed upon inhibition of ER mannosidase I. *J. Biol. Chem.* 2000; 275:40757-40764.
16. Kuliawat R, Prabakaran D, Arvan P. Proinsulin endoproteolytic activity confers enhanced targeting of processed insulin to the regulated secretory pathway. *Mol. Biol. Cell* 2000; 11:1959-1972.
17. Zhang B-Y, Chang A, Kjeldsen T, Arvan P. Intracellular retention of newly-synthesized insulin in yeast is caused by endoproteolytic processing in the Golgi complex. *J. Cell Biol.* 2001; 153:1187-1197.
18. Arvan P, Zhang B-y, Feng L, Liu M, Kuliawat R. Luminal protein multimerization in the distal secretory pathway/secretory granules. *Curr. Opin. Cell Biol.* 2002; 14:448-453.
19. Arvan P, Zhao X, Ramos-Castañeda J, Chang A. Secretory pathway quality control operating in Golgi, plasmalemmal, and endosomal systems. *Traffic* 2002; 3:771-780.
20. Zhang B-Y, Liu M, Arvan P. Behavior in the eukaryotic secretory pathway of insulin-containing fusion proteins and single-chain insulins bearing various B-chain mutations. *J. Biol. Chem.* 2003; 278: 3687-93.
21. Liu, M., J. Ramos-Castañeda, and P. Arvan. 2003. Role of the connecting peptide in insulin biosynthesis. *J. Biol. Chem.* 2003; 278:14798-14805.
22. Feng L, Arvan P. The trafficking of alpha 1-antitrypsin, a post-Golgi secretory pathway marker, in INS-1 pancreatic beta cells. *J. Biol. Chem.* 2003; 278:31486-31494.
23. Arvan P, Halban PA. Sorting ourselves out: seeking consensus on trafficking in the beta cell. *Traffic* 2004; 5:53-61.
24. Kuliawat R, Kalinina E, Bock J, Fricker L McGraw TE, Zhong J, Scheller RH, Arvan P. Syntaxin-6 SNARE involvement in secretory and endocytic pathways of cultured pancreatic beta cells. *Mol. Biol. Cell.* 2004; 15:1690-1701.
25. Park YN, Arvan P. The acetylcholinesterase-homology region is essential for normal conformational maturation and secretion of thyroglobulin. *J. Biol. Chem.* 2004; 279:17085-17089.
26. Ramos-Castañeda J, Park YN, Liu M, Hauser K, Rudolph H, Shull GE, Jonkman MF, Mori K, Ikeda S, Ogawa H, Arvan P. Deficiency of ATP2C1, a Golgi ion pump, induces secretory pathway defects in ER-associated degradation and sensitivity to ER-stress. *J Biol Chem.* 2005; 280:9467-9473.
27. Liu M, Li Y, Cavener D, Arvan P. Proinsulin disulfide maturation and misfolding in the endoplasmic reticulum. *J Biol Chem.* 2005 14:13209-13212.
28. Kuliawat R, Ramos-Castañeda J, Liu Y, Arvan P. Intracellular trafficking of thyroid peroxidase to the cell surface. *J. Biol. Chem.* 2005; 280:27713-27718.
29. Di Jeso B, Park Y-N, Ulianich L, Treglia AS, Urbanas ML, High S, Arvan P. Mixed-disulfide folding intermediates between thyroglobulin and ER resident oxidoreductases ERp57 and PDI. *Mol. Cell Biol.* 2005; 25:9793-9805.
30. Forster, ML, Sivick K, Park Y-P, Arvan P, Lencer WI, Tsai B. PDI-like proteins play opposing roles during retro-translocation. *J. Cell Biol.* 2006; 173:853-859.
31. Menon S, Abplanalp WA, Yoo S-E, Agui T, Furudate S-i, Kim PS, Arvan P. Oxidoreductase interactions include a role for ERp72 engagement with mutant thyroglobulin from the rdw/rdw rat dwarf. *J. Biol. Chem.* 2007; 282:6183-6191.
32. Lara-Lemus R, Liu M, Turner M, Scherer P, Stenbeck G, Iyengar P, Arvan P. Luminal protein sorting to the constitutive secretion pathway of a regulated secretory cell. *J. Cell Sci.* 2006; 119:1833-1842.
33. Liu M, Hodish I, Rhode CJ, Arvan, P. Proinsulin maturation, misfolding and proteotoxicity. *Proc Natl Acad Sci U S A.* 2007; 40:15841-15846.
34. Zhao X, Nothwehr S, Lara-Lemus R, Zhang BY, Peter H, Arvan P. Dominant-negative behavior of mammalian Vps35 in yeast requires a conserved PRLYL motif involved in retromer assembly. *Traffic* 2007; 8:1829-40.
35. Restrepo R, Zhao X, Peter H, Zhang BY, Arvan P, Nothwehr SF. Structural features of vps35p involved in interaction with other subunits of the retromer complex. *Traffic* 2007; 8:1841-1853.

36. Kim PS, Jongsamak P, Menon S, Li B, Hossain SA, Bae J-H, Panijpan B, Arvan P. Defective protein folding and intracellular retention of thyroglobulin-R19K mutant as a cause of human congenital goiter. *Mol. Endocrinol.* 2008; 22:477-484
37. Colombo C, Porzio O, Liu M, Massa O, Vasta M, Salardi S, Beccaria L, Monciotti C, Toni S, Pedersen O, Hansen T, Federici L, Pesavento R, Cadario F, Federici G, Ghirri P, Arvan P, Iafusco D, Barbetti F; Early Onset Diabetes Study Group of the Italian Society of Pediatric Endocrinology and Diabetes (SIEDP). Seven mutations in the human insulin gene linked to permanent neonatal/infancy-onset diabetes mellitus. *J. Clin. Invest.* 2008; 118:2148-56.
38. Yamaguchi Y, Larkin D, Lara-Lemus R, Ramos-Castañeda J, Liu M, Arvan P. Endoplasmic reticulum (ER) chaperone regulation and survival of cells compensating for deficiency in the ER stress response kinase, PERK. *J. Biol. Chem.* 2008; 283:17020-9.
39. Lee J, Di Jeso B, Arvan P. The cholinesterase-like domain of thyroglobulin functions as an intramolecular chaperone. *J. Clin. Invest.* 2008; 118:2950-58.
40. Rajpal G, Liu M, Zhang Y, Arvan P. Single-chain insulins as receptor agonists. *Mol. Endocrinol.* 2009; 23: 679-88.
41. Lee J, Wang X, Di Jeso B, Arvan P. The cholinesterase-like domain of thyroglobulin, essential for trafficking in the secretory pathway, is required for protein dimerization. *J. Biol. Chem.* 2009; 284:12752-61.
42. Hodish I, Liu M, Rajpal G, Larkin D, Holz R, Adams A, Liu L, Arvan P. Misfolded proinsulin affects bystander proinsulin in neonatal diabetes. 2009; Manuscript submitted.
43. Rajpar MH, McDermott B, Kung L, Eardley R, Knowles L, Heeran M, Thornton DJ, Wilson R, Bateman JF, Poulosom R, Arvan P, Kadler KE, Briggs MD, Boot-Handford RP. Targeted induction of Endoplasmic Reticulum stress induces cartilage pathology. 2009; Manuscript submitted to PLoS Genetics.
44. Liu M, Haataja L, Wright J, Barbetti F, Weiss MA, Arvan P. Proinsulin misfolding as a cause of neonatal diabetes mellitus. Manuscript in preparation .

### **C. Research Support**

#### **Ongoing Research Support**

R01 DK40344-21 (PI – P. Arvan)

04/01/2009-03/31/2013

National Institutes of Health

"Thyocyte protein transport to the cell surface"

The long term objective of this project is to investigate how protein trafficking in the secretory pathway of thyroid epithelial cells provides a basis for the synthesis and secretory of thyroid hormone, and how this may go awry in various thyroid disease states.

Role: PI

R01 DK 048280-16 (PI – P. Arvan)

07/01/2009-06/30/2014

National Institutes of Health

"Peptide Hormone Sorting to the Secretory/Storage Granule"

The long term objective of this project is to investigate the mechanism(s) of formation and maturation of the secretory granule. All studies in this grant involve regulated secretory cells that make granules, using the pancreatic beta cell as the prototype.

Role: PI

R01 DK069764-02

12/01/2004-11/30/2009

Prime Sponsor: National Institutes of Health (PI – M. Weiss)

Direct Sponsor: Case-Western Reserve University

"Folding of Proinsulin"

Collaborative studies on non-foldable proinsulins.

Role: Subcontract PI – P. Arvan

#### **Completed Research Support**

None