

BIOGRAPHICAL SKETCH

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NAME Kaufman, Randal J.		POSITION TITLE Professor, Department of Biological Chemistry Investigator, Howard Hughes Medical Institute	
eRA COMMONS USER NAME (credential, e.g., agency login) kaufmanr			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of Colorado, Boulder, CO	B.A.	1972	Mol. Cell & Dev. Biology
Stanford University, Palo Alto, CA	Ph.D.	1979	Pharmacology
Center for Cancer Research, Mass.Inst. Tech, Cambridge, MA (Fellow, Helen Hay Whitney)		1979-1982	Mol. Biol. & Virology

A. Positions and Honors.

- 1982-1986 **Senior Scientist**, Genetics Institute, Cambridge, MA
 1986-1993 **Director**, Molecular and Cellular Genetics, Genetics Institute, Cambridge, MA
 1988-1989 Ad Hoc member, NIH Genetics Study Section for SBIR grants
 1990-1995 Member, NHLBI Hematology II Study Section
 1990-1995 Blood, Editorial Board Member
 1991-'96; '97-02 Journal of Biological Chemistry, Editorial Board Member
 1991-2001 Molecular and Cellular Biology, Editorial Board Member
 1992 Reviewer, NHLBI Program Project RFA in Thrombosis
 1992-1997 Thrombosis Research, Editorial Board Member
 1993-present **Professor**, Department of Biological Chemistry, University of Michigan, Ann Arbor, MI
 1993-present **Investigator**, Howard Hughes Medical Institute, University of Michigan, Ann Arbor, MI
 1996- Member, Medical & Scientific Advisory Committee, National Hemophilia Foundation
 1997- Special Reviewer, NIH Molecular Cytology Study Section
 2005 Ad Hoc member, NIH Membrane Biology & Protein Processing Study Section
 1998-present Journal of Thrombosis and Haemostasis, Editorial Board Member
 1993 Dr. Murray Thelin Award, National Hemophilia Foundation
 1998 International Association Francaise Des Hemophiles Award "Prix Henri Chaigneau"
 1999 Investigator Recognition Award, International Society for Thrombosis and Haemostasis
 2000 Distinguished Investigator Award, Michigan Hemophilia Society.
 2003 Van Wezel Prize, European Society of Animal Cell Technology (ESACT)
 2004-present **Professor**, Internal Medicine, University of Michigan, Ann Arbor, MI
 2005-present Warner-Lambert / Parke-Davis Distinguished Professor of Medicine

B. Selected peer-reviewed publications (from 250 original publications and 115 reviews / chapters).

- Hu, P, Han, Z, Couvillon, AD, **Kaufman, RJ**, Exton, JH. (2006) Autocrine tumor necrosis factor alpha links endoplasmic reticulum stress to the membrane death receptor pathway through IRE1 α -mediated NF- κ B activation and down-regulation of TRAF2 expression. *Mol. Cell Biol.* 26 (8):3071-84.
- Back, SH, Lee, K, Vink, E, **Kaufman, RJ**. (2006) Cytoplasmic IRE1 α -mediated XBP1 mRNA splicing in the absence of nuclear processing and ER stress. (2006) *J. Biol. Chem.* 281(27):18691-18706 .
- Scheuner, D, Wang, F, Patel, R, Lee, K, Kumar, K, Karin, M, **Kaufman, RJ**. (2006) dsRNA-dependent protein kinase phosphorylation of the alpha subunit of eukaryotic translation initiation factor 2 mediates apoptosis. *J. Biol. Chem.* 281(30):21458-68.
- Denoyelle, C, Abou-Rjaily, G, Bezrookove, V, Verhaegen, M, Johnson, TM, Fullen, DR, Pointer, JN, Gruber, SB, Su, LD, Nikiforov, M, **Kaufman, RJ**, Bastian, BC, Soengas, M. (2006) Anti-oncogenic role of the endoplasmic reticulum differentially acxtivated by mutations in the MAPK pathway. *Nature Cell Biology* 8(10):1053-1063.

- Zhou, J, Liu, CY, Back, SH, Clark, RL, Peisach, D, Xu, Z, **Kaufman, RJ**. (2006) The structure of an unfolded protein response sensor reveals a novel dimerization interface required for IRE1 and PERK activation. *Proc. Natl. Acad. Sci. U.S.A.* **103**(39): 14343-14348.
- Mazroui, R, Sukarieh, R, Bordeleau, ME, **Kaufman, RJ**, Northcote, P, Tanaka, J, Gallouzi, I, Pelletier, J. (2006) Inhibition of ribosome recruitment induces stress granule formation independent of eIF2{alpha} phosphorylation. *Mol. Biol. Cell* **17**(10): 4212-4219.
- Robert, F, Kapp, LD, Khan, SN, Acker, M, Kolitz, S, Kazemi, S, **Kaufman, RJ**, Merrick, WC, Koromilas, AE, Lorsch, JR, Pelletier, J. (2006) Initiation of Protein synthesis by hepatitis C virus is refractory to reduced eIF2*GTP*Met-tRNAiMet ternary complex availability. *Mol. Biol. Cell* **17**(11): 4632-44.
- Fribley, AM, Evenchik, B, Zeng, Q, Park, BK, Guan, JY, Zhang, H, Hale, TJ, Soengas, MS, **Kaufman, RJ**, Wang, CY. (2006) Proteasome inhibitor PS-341 induces apoptosis in cisplatin-resistant squamous cell carcinoma cells by induction of Noxa. *J. Biol. Chem.* **281**(42): 31440-7.
- Nyfelner, B, Zhang, B, Ginsburg, D, **Kaufman, RJ**, Hauri HP. (2006). Cargo selectivity of the ERGIC-53/MCFD2 transport receptor complex. *Traffic* **7**(11): 1473-81.
- Rutkowski, DT, Arnold, SM, Miller, CN, Wu, J, Li, J, Gunnison, KM, Mori, K, Sadighi Akha, AA, Raden, D, **Kaufman, RJ**. (2006) Adaptation to ER stress is mediated by differential stabilities of pro-survival and pro-apoptotic mRNAs and proteins. *PLOS Biol.* **4**(11): e374.
- Mierde, DV, Scheuner, D, Quintens, R, Patel, R, Song, B, Tsukamoto, K, Beullens, M, **Kaufman, RJ**, Bollen, M, Schuit, FC. (2006) Glucose activates a PP1-inhibitor-1 signaling pathway to enhance overall translation in pancreatic beta cells. *Endocrinology* **148**(2): 609-617.
- Kouroku, Y, Fujita, E, Tanida, I, Ueno, T, Isoai, A, Kumagai, H, Ogawa, S, **Kaufman, RJ**, Kominami, E, Momoi, T. (2007) ER stress (PERK/eIF2alpha phosphorylation) mediates the polyglutamine-induced LC3 conversion, an essential step for autophagy formation. *Cell Death Differ.* **14**(2): 230-239.
- Zhu, A, Sun, H, Raymond Jr, R, Furie, BC, Furie, B, Bronstein, M, **Kaufman, RJ**, Westrick, R, Ginsburg, D. (2007) Fatal hemorrhage in mice lacking γ -glutamyl carboxylase. *Blood* **109**(12): 5270-5275.
- Nagasawa, K, Higashi, T, Hosokawa, N, **Kaufman, RJ**, Nagata K. (2007) Simultaneous induction of the four subunits of the mammalian TRAP complex by ER stress accelerates ER degradation of misfolded proteins. *EMBO Reports* **8**(5): 483-489.
- Shang, J, Gao, N, **Kaufman, RJ**, Ron, D, Harding, HP, Lehrman MA. (2007) Translation attenuation by PERK balances ER glycoprotein synthesis with lipid-linked oligosaccharide flux. *J. Cell Biol.* **176**(5): 605-616.
- Costa-Mattioli, M, Gobert, D, Stern, E, Gamache, K, Colina, R, Cuello, C, Sossin, W, **Kaufman, RJ**, Pelletier, J, Rosenblum, K, Krnjevic, K, Lacaille, JC, Nader, K, Sonenberg, N. (2007) eIF2alpha phosphorylation bidirectionally regulates the switch from short- to long-term synaptic plasticity and memory. *Cell* **129**(1): 195-206.
- Mazroui, R, Di Marco, S, **Kaufman, RJ**, Gallouzi, IE. (2007) Inhibition of the ubiquitin-proteasome system induces stress granule formation. *Mol. Biol. Cell* **8**(7): 2603-2618.
- Soldà, T, Galli, C, **Kaufman, RJ**, Molinari, M. (2007) Substrate specific requirements for UGT1-dependent release from calnexin. *Mol. Cell* **27**(2): 238-249.
- Drogat, B, Auguste, P, Nguyen, DT, Bouche-careilh, M, Pineau, R, Nalbantoglu, J, **Kaufman, RJ**, Chevet E, Bikfalvi, A, Moenner, M. (2007) IRE1 signalling is essential for ischemia-induced vascular endothelial growth factor-A expression and contributes to angiogenesis and tumor growth *in vivo*. *Cancer Res.* **67**(14): 6700-6707.
- Rutkowski, DT, Kang, SW, Goodman, AG, Garrison, JL, Taunton, J, Katze, MG, **Kaufman, RJ**, Hegde, RS. (2007) The role of p58^{IPK} in protecting the stressed endoplasmic reticulum. *Mol. Biol. Cell* **18**(9): 3681-3691.
- Renna, M, Caporaso, MG, Bonatti, S, **Kaufman, RJ**, Remondelli, P. (2007) Regulation of ergic-53 gene transcription in response to endoplasmic reticulum stress. *J. Biol. Chem.* **282**(31): 22499-512.
- Wu, J, Rutkowski, DT, Dubois, M, Swathirajan, J, Saunders, T, Wang, J, Song, B, Yau, GDY, **Kaufman, RJ**. (2007) ATF6 alpha optimizes long-term endoplasmic reticulum function to protect cells from chronic stress. *Developmental Cell* **13**(3): 351-64.
- Cerullo, V, Seiler, MP, Mane, V, Cela, R, Clarke, C, **Kaufman, RJ**, Pipe, SW, Lee, B. (2007) Correction of Murine Hemophilia A and Immunological Differences of Factor VIII Variants Delivered by Helper-dependent Adenoviral Vectors. *Mol. Ther.* **15**(12): 2080-7.

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- Sakaki K, Wu J, Kaufman RJ (2008) Protein kinase C-theta is required for autophagy in response to stress in the endoplasmic reticulum. *J Biol Chem* (online preprint)
- Scheuner D, Kaufman RJ (2008) The Unfolded Protein Response: A Pathway That Links Insulin Demand with β -Cell Failure and Diabetes. *Endocr Rev* (online preprint)
- Zhang B, Spreafico M, Zheng C, Yang A, Platzer P, Callaghan MU, Avci Z, Ozbek N, Mahlangu J, Haw T, **Kaufman RJ**, Marchant K, Tuddenham EG, Seligsohn U, Peyvandi F, Ginsburg D. (2008) Genotype-phenotype correlation in combined deficiency of factor V and factor VIII. *Blood* **111**(12): 5592-600
- Sakaki K, Wu J, **Kaufman RJ**. (2008) Protein kinase Ctheta is required for autophagy in response to stress in the endoplasmic reticulum. *J. Biol. Chem.* **283**(22): 15370-80. Zhang, K., **Kaufman, R.J.** (2008) Identification and characterization of ER stress-induced apoptosis *in vivo*. *Methods in Enzymology.* **442**:395-419.
- Zhang K, **Kaufman RJ**. (2008) From Endoplasmic Reticulum Stress to the Inflammatory Response. *Nature.* **454**(7203):455-62.
- Song B, Scheuner D, Ron D, Pennathur S, **Kaufman RJ**. (2008) Genetic deletion of C/EBP homologous protein CHOP reduces oxidative stress, improves beta cell function and prevents apoptosis. *J. Clin. Invest.* **118**:3378-3389.
- Malhotra JD, Miao H, Zhang K, Wolfson A, Pennathur S, Pipe SW, **Kaufman RJ**. (2008) Antioxidants reduce endoplasmic reticulum stress and improve protein secretion. *Proc Natl Acad Sci U S A* **105**:18525-30.
- Rutkowski DT, Wu J, Back S-H, Clark R, Ferris SP, Song S, Iqbal J, Goodman A, Katze MG, Hussain M, Swathirajan J, Wang J, Yau GD-Y, **Kaufman RJ**. (2008) UPR pathways combine to prevent dysregulation of lipid metabolism caused by suppression of transcriptional master regulators. *Dev Cell* **15**(6): 829-40.
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- Wang J, Farr G, Zeiss C, Gill DR, Wilson J, Furtak K, Rutkowski D, **Kaufman RJ**, Ruse C, Yates III JR, Perrin S, Feany M, Horwich A. (2009) Progressive aggregation despite chaperone associations of a mutant SOD1-YFP in transgenic mice that develop ALS. *Proc. Natl. Acad. Sci.* (In Press).
- Bommasamy H, Back S-H, Lee K, Meshinch S, Vink E, Sriburi R, Frank M, Jackowski S, **Kaufman RJ**, Brewer JW. (2009) ATF6 α and induction of XBP-1-independent expansion of the endoplasmic reticulum. *J. Cell. Sci.* (In Press). (* equal contribution, ^ corresponding authors)

C. Research Support.

Ongoing Research Support

- Howard Hughes Medical Institute (Kaufman-PI) 09/01/93 – 08/31/10
Howard Hughes Medical Institute
Regulation of Protein Synthesis, Processing and Secretion
Although HHMI supports Dr. Kaufman as an HHMI Investigator, these funds are not awarded to a specific research proposal or project.
- P01 HL057346 (Ginsburg, Kaufman-PI Proj 2) 12/01/96 – 03/31/14
NIH/NHLBI
How Does FVIII Expression Induce Cell Death
The major goals of this project are:
1. How does oxidative stress inhibit FVIII folding and secretion.
 2. Test interventions to reduce ER stress, facilitate FVIII folding, and/or improve ER function for therapeutic benefit during hemophilia A gene therapy.
- R37 DK042394 MERIT STATUS (Kaufman-PI) 07/01/97 – 8/31/12
NIH/NIDDK
Unfolded Protein Response in Beta Cells
1. Translational control through eIF2 α phosphorylation maintains β cell function to prevent diabetes.

2. IRE1 and ATF6 are essential to coordinate requirements for insulin production with ER expansion in β cells.
3. Intervention to improve proinsulin folding and/or reduce oxidative stress will improve β cell function and have therapeutic benefit in diabetes

R01 HL052173 (Kaufman-PI)

08/01/95– 11/30/10

NIH/NNHLBI

Regulation of Factor VIII Secretion

1. Determine how accumulation of FVIII within the ER activates the UPR and induces apoptotic cell death.
2. Elucidate the role of glycoprotein quality control in the secretion of FVIII
3. Identify the mechanism by which the ERGIC-53/MCDF2 complex transports FV and FVIII for the ER to the cis-Golgi compartment.

R01 HL82619 (Pipe, Kaufman-Col)

09/1/05 – 08/31/09 NCX 08/31/10

NIH/NHF response to RFA-HL-04-032

Factor VIII Bioengineered for Improved Secretion Efficiency, Potency and Stability

1. Factor VIII bioengineered for improved secretion efficiency will lead to more efficient production of a FVIII therapeutic
2. FVIII bioengineered for resistance to inactivation will lead to a FVIII therapeutic with higher potency and stability

U025056 (Sartor/Kaufman, Co-PIs)

2/1/2009 – 1/31/2010

UM Center for Computational Biology (CCMB) Pilot Research Grant Program

Understanding the role of ATF4 in translational regulation under ER-stress through ChIP-Seq and a novel integrative approach.

1. Identification of genome-wide ATF4 binding sites using ChIP-Seq, and currently-used, as well as a novel proposed, peak scoring methods
2. Assess biological significance of results and compare methodologies by a) integration of identified peaks with in-parallel expression data, b) overlap between treated and untreated ATF4 results and with previous CHOP binding results, c) motif-identification within peaks, and d) functional enrichment/molecular concept mapping analysis

R03 MH089782 (Kaufman-PI)

09/30/09 – 05/31/10

NIH/NIMH

HTP chemical genomic screens to identify positive regulators of the Unfolded Protein Response

The major goals of this project are:

1. Use a cell-based assay to identify small molecules that activate XBP1 splicing to enhance the adaptive arm of the UPR.
2. Use a cell-based assay to identify small molecules that activate CHOP gene expression to exacerbate the cell death arm of the UPR.

Completed Research Support

R03 MH084182 (Kaufman-PI)

06/01/08 – 05/31/09

NIH/NIMH

High Throughput Chemical Genomics to Identify Novel Inhibitors of CHOP

The major goals of this project are to use cell-based assays in high throughput screens (HTS) to identify small molecules that inhibit CHOP to regulate the UPR and ameliorate diseases of protein misfolding

Human Frontiers Science Program (Lindqvist/Kaufman)

07/01/05 – 06/30/08 NCX 12/31/08

HFSP

The function of glycoprotein receptors in the transit from ER to Golgi

The major goal of this project is to determine the structure and function of ERGIC53/MCFD2 with clotting factors

R01 DK065980 (Xu)

09/20/03 – 07/31/06

NIH/NIDDK

Structure and Function in the Unfolded Protein Response

1. To elucidate the structure of the UPR sensor IRE1.
2. Determine the molecular mechanism of UPR activation through PERK, IRE1, and ATF6.