BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Michael S. Goligorsky	Professor of Medicine and Physiology
eRA COMMONS USER NAME (credential, e.g., agency login) Michael S. Goligorsky	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Kiev Medical Institute (former USSR)	MD	1970	Medicine & Surgery
Kiev Medical Institute (former USSR)	PhD	1973	Physiology

Please refer to the application instructions in order to complete sections A, B, C, and D of the Biographical Sketch.

A. PERSONAL STATEMENT

My deep interest in vascular pathobiology is unflagging. For the past > than 10 years my laboratory was investigating vasculopathy associated with various cardiovascular risk factors – esp, ADMA, homocysteine, and AGE-modified proteins. Having started with Zucker diabetic fat rats, we described the time course of developing macro- and microvascular abnormalities, disclosed the pathogenetic role of oxidative and nitrosative stress resulting in the accumulation of peroxynitrite and established the curative effect of a selenorganic antioxidant and peroxynitrite scavenger, ebselen (*US Patent No. US 6,967,219 B2* – Reversing or preventing premature vascular senescence). *In vitro* studies revealed the role of non-enzymatically glycated modification of long-lived protein (collagen I) in engaging $p16^{INK4a}$ and $p21^{CIP1}$ pathways to induction of premature senescence of endothelial cells, lysosomal dysfunction and ganglioside accumulation in prematurely senescent endothelial cells, lipid mediators of autophagy in stress-induced premature senescence of endothelial cells, and described abnormalities of autophagic processes as a key mediator of stress-induced premature senescence (SIPS). Further *in vivo* studies in db/db mice demonstrated that adoptive transfer of syngeneic bone marrow-derived cells improves macro- and microvasculopathy. Using this animal model, we arrived to a conclusion that endothelial progenitor cells become functionally incompetent due to the reduced resistance to oxidative stress and demonstrated that ebselen restores stem cell competence both *in vivo* and *ex vivo*. These studies wer4e presented at 2 Gordon conferences and multiple nephrology and vascular biology conferences.

Most recent work has established oxidative stress to be a potent inhibitor of the expression of a key NAD-dependent deacetylase sirtuin-1 (SIRT1), a precursor of SIPS, disclosed that genetic manipulation of SIRT1 facilitates cell fate decisions, and that ebselen *per se* prevents stress-induced decline in SIRT1. My lab has now generated or acquired from other investigators multiple tools to pursue the main goals of the current proposal: to explore the mechanisms of dysregulation of SIRT1, dissect main components of developing lysosomal dysfunction – collapse of pH gradient, lysosomal membrane permeabilization, and release of cathepsins, and test previously devised strategies to repair abnormal SIRT1, thus correcting SIPS and attendant macro- and microvasculopathy. These questions will be addressed using cell cultures and mice with endothelial deletion of SIRT1. It is my hope that the subject matter is of substantial novelty and import to vascular pathobiology and that our laboratory with a more than a decade-long accumulated expertise is uniquely positioned to tackle these questions.

B. EMPLOYMENT

Research and Professional Experience:

1975-1978 Assistant Professor, Kiev Medical Institute, USSR
1978-1980 Associate Professor, Kiev Medical Institute, USSR

1983-1984 Lecturer and Sr. Nephrologist, Soroka Medical Center, Ben Gurion University, Israel
1982-1983 Visiting Scientist, Yale University
1984-1988 Postdoctoral Fellow, Washington University
1988-1992 Assistant Professor of Medicine, SUNY at Stony Brook
1992-1997 Associate Professor of Medicine and Physiology, SUNY Stony Brook
1997-2002 Professor of Medicine and Physiology, SUNY Stony Brook
1998-date Honorary Professor, University College London, UK
2002-date Professor of Medicine, Pharmacology and Physiology, New York Medical College, Valhalla, NY

HONORS: 1991 – elected to the American Society of Clinical Investigations; 2002 – elected to the Association of American Physicians. *Associate Editor*: Am J Pathology, Am J Physiology: Cell; Nephrol Dial Transplant Member of the *Editorial Board*: Am J Physiol: Renal; J Am Soc Nephrol, Microvasc Res, Kidney Internat.

C. SELECTED PEER-REVIEWED PUBLICATIONS (from a list of 215 publications)

Gealikman O, SV Brodsky, F Zhang, P Chander, C Friedli, A Nasjletti, MS Goligorsky Angiogenic incompetence and microvasculopathy in the Zucker diabetic fat rat are ameliorated with Ebselen treatment: endothelial dysfunction as a modifier of angiogenic response. Kidney Int. 66: 2337-2347, 2004. **PMID15569234**

Chander P, O Gealekman, SV Brodsky, S Elitok, A Tojo, M Crabtree, SS Gross, MS. Goligorsky. Nephropathy in Zucker diabetic fat rat is associated with oxidative and nitrosative stress: prevention by chronic therapy with a peroxynitrite scavenger ebselen. J Am Soc Nephrol, 15: 2391-2403, 2004. **PMID15339988**

Elitok S, S Brodsky, D Patschan, K Lerea, MS Goligorsky. Cyclic RGD peptide inhibits macrophage infiltration of the kidney and carotid artery lesions in ApoE-deficient mice. Am J Physiol: Renal 290: F159-F166, 2006. **PMID16106036**

Patschan S, H Li, S Brodsky, D De Angelis, MS Goligorsky. Probing endothelial lipid rafts with proximity imaging: effects of pro-atherogenic factors. Am J Physiol: Heart, 290: H2210-H2219, 2006. **PMID15321365**

Chen J, J Eskander, D Galicka, Z Darzynkiewicz, MS Goligorsky. Contribution of $p16^{INK4a}$ and $p21^{CIP1}$ pathways to induction of premature senescence of human endothelial cells: permissive role of p53. Am J Physiol: Heart 290: H1575-H1586, 2006. **PMID16243918**

Chen J, MS Goligorsky. Premature senescence of endothelial cells: Methusaleh's dilemma. Am J Physiol 290: H1729-H1739, 2006. **PMID16603702**

O'Riordan E, N Mendelev, S Patschan, P Chander, MS Goligorsky. Chronic NOS inhibition actuates endothelial-mesenchymal transformation. Am J Physiol: 292: H285-H294, 2007. **PMID16963618**

Patschan S, J Chen, O Gealekman, K Krupincza, M Wang, L Shu, JA. Shayman, MS Goligorsky – Mechanisms of premature cell senescence: lysosomal dysfunction and ganglioside accumulation in endothelial cells. Am J Physiol: Renal, 294: 100-109, 2008. **PMID17928415**

Patschan S, J Chen, A Polotskaia, N Mendelev, J Cheng, D Patschan, MS Goligorsky - Lipid mediators of autophagy in stress-induced premature senescence of endothelial cells. Am J Physiol: Heart, 294: H1119-H1129, 2008. **PMID18203850**

Chen J, Park H-C, Patschan S, Brodsky SV, Gealikman O, Kuo M-C, Li H, Addabbo F, Zhang F, Nasjletti A, Gross SS, Goligorsky MS. Premature vascular senescence in metabolic syndrome: Could it be prevented and reversed by a selenorganic antioxidant and peroxynitrite scavenger ebselen? Drug Discovery Today: Therapeutic strategies – Renal diseases. 2007, 4(1):93-99. **PMID18496595**

Chen J, Patschan S, Goligorsky MS. Stress-induced premature senescence of endothelial cells. J Nephrol 21: 337-344, 2008. **PMID18587721**

Chen J, H Li, F Addabbo, F Zhang, E Pelger, D Patschan, HC, MC Kuo, G Gobe, A Nasjletti, MS Goligorsky. Adoptive transfer of syngeneic bone marrow-derived cells in mice with obesity-induced diabetes: selenoorganic antioxidant ebselen restores stem cell competence. Am J Pathol, 174: 701-711, 2009. **PMCID2630577**

Patschan S, MS Goligorsky. Autophagy: The missing link between non-enzymatically glycated proteins inducing apoptosis and premature senescence of endothelial cells ? Autophagy, 4:4, 521-3, 2008. **PMID18367870**

Goligorsky MS, J Chen, S Patschan. Stress-induced premature senescence of endothelial cells – a perilous state between recovery and point of no return. Curr Opin Hematol, issue on Vascular Biology 16: 215-219, 2009. **PMID1931892 PMC Journal in process.**

Yasuda K, HC Park, B Ratliff, F Addabbo , AK Hatzopoulos, P Chander, MS Goligorsky. Adriamycin nephropathy – a failure of endothelial progenitor cell-induced repair (Am J Pathol, in press, 2010)

US Patent No. US 6,967,219 B2 awarded to SS Gross and MS Goligorsky – **Reversing or preventing premature vascular senescence** (Nov 22, 2005)

D. RESEARCH SUPPORT

ACTIVE GRANT SUPPORT

RO1 DK45462 (Goligorsky, PI) 01/07/05 – 04/30/15
NIH/NIDDK: ***Endothelial Dysfunction, Nitric Oxide and Renal Failure***
The major goal of this project is to investigate the possibility of endothelial-mesenchymal transformation in progression of chronic renal disease. **This grant has been competitively renewed, budget and duration pending.**

RO1 DK084394 (Goligorsky, PI) 07/01/09 – 06/30/14
NIH/NIDDK: **Weibel-Palade bodies – sentinels of acute ischemia**.
This project is designed to address the role of exocytosis of Weibel-Palade bodies in mobilization of stemcells and induction of proinflammatory mediators.

COMPLETED GRANT SUPPORT FOR PREVIOUS THREE (3) YEARS:

R01 DK042783 (Goligorsky, PI) 08/01/97 – 11/30/07
NIH/DIDDK: **Endothelial dysfunction in acute renal ischemia**
The major goal of this grant was to detect manifestations of endothelial dysfunction an elucidate its mechanisms in acute renal ischemia.

RO1 DK054602 (Goligorsky, PI) 01/01/99 through 31/12/10
NIH/NIDDK: ***Prevention of Vasculopathy and Nephropathy in Metabolic Syndrome***
(Former title: Angiogenesis and vascular permeability in diabetic nephropathy)
This grant application intends to examine the mechanisms of macro- and micro vasculopathy in Zucker diabetic fatty rats and investigate the potential of peroxynitrite scavenging in preventing and reversing these complications.

R21 DK71647 (PI: J Stewart; Co-PI: MS Goligorsky) 04/01/06 – 03/31/09
Non-invasive diagnosis of endothelial cell dysfunction in ESRD patients
The major goal of this project is to continue our exploration of laser Doppler flowmetry as a non-invasive tool to predict and diagnose endothelial dysfunction in patients with chronic kidney disease.

R44 HL074524(PI: L Montgomery; Co-PI: MS Goligorsky) 08/01/06 – 07/31/08
Measuring Intra/Extracellular Volume and Hemodynamics
This project seeks to evaluate the validity and usefulness of a novel technology to measure fluctuations in body electrical impedance during hemodialysis