FACULTY CURRICULUM VITAE

Alexander Shnyra MD, PhD

I. EDUCATION:

Year	Degree	Institution
1976	BS Biophysics	Pirogov Medical Institute. Moscow, USSR
1979	MD	Pirogov Medical Institute. Moscow, USSR

II. POSTGRADUATE EDUCATION:

Year	Degree	Institution
1985	PhD Biochemistry	All-Union Cardiology Research Center, Academy of Medical Sciences of the USSR, Moscow, USSR

III. ACADEMIC APPOINTMENTS:

Year	Position	Institution
2007-present	Associate Professor	Dept. of Pharmacology and Microbiology, Kansas City University of Medicine and Biosciences, Kansas City, MO, USA
2000-2007	Assistant Professor	Dept. of Basic Medical Science, University of Missouri-Kansas City, Kansas City, MO, USA
1995 - 1999	Research Assistant Professor	Dept. of Microbiology, Molecular Genetics and Immunology, The University of Kansas Medical Center, Kansas City, KS, USA
1992-1995	Assistant Professor	Dept. of Emergency and Critical Care Medicine, Faculty of Medicine, U.A.E. University, Al Ain, United Arab Emirates

1989-1992	Visiting Scientist	Dept. of Clinical Bacteriology, Karolinska Institute, Stockholm, Sweden
1988-1989	Senior Scientist	Dept. of Cell and Molecular Biology, All-Union Cardiology Research Center, Academy of Medical Sciences of the USSR, Moscow, USSR
1985-1988	Postdoctoral Fellow Cell Biology	Dept. of Cell and Molecular Biology, All-Union Cardiology Research Center, Academy of Medical Sciences of the USSR, Moscow, USSR

IV. PROFESSIONAL EXPERIENCE:

Teaching: Have been consistently judged excellent in undergraduate and postgraduate teaching by colleagues and students (Immunology, Microbiology, and Biochemistry)

Research: Have developed several funded research projects in Soviet Union, Sweden, United Arab Emirates and the United States.

Administration: Have been a Director of Research Laboratories at the Department of Emergency and Critical Care Medicine, U.A.E. University and UMKC School of Medicine. Have completed successfully and built a modern research laboratory for the Departments.

V. PROFESSIONAL SOCIETIES AND AFFILIATIONS:

Year	**Organization**	**Office**
1994-present	American Association for the Advancement of Science	1333 H Street NW Washington, DC 20005
1996-present	International Endotoxin and Innate Immunity Society	3901 Rainbow Blvd. Kansas City, KS 66160
1999-present	Society for Leukocyte Biology	9650 Rockville Pike Bethesda, MD 20814-3998
2000-present	American Association of Immunologists	9650 Rockville Pike Bethesda, MD 20814-3994
2006	The New York Academy of Sciences	7 World Trade Center 250 Greenwich Street, 40th floor New York, NY 10007-2157

VI. HONORS AND AWARDS:

THE SILVER MEDAL OF THE EXHIBITION OF NATIONAL ACHIEVEMENTS OF THE USSR, Moscow, November 1988

THE YOUNG RESEARCH AWARD OF THE INTERNATIONAL SOCIETY FOR ARTIFICIAL ORGANS, October 1989 (Japan)

RESEARCH FELLOWSHIP IN IMMUNOLOGY, Human Frontier Science Program, Strasbourg, France, January 1993

MARQUIS "WHO IS WHO IN THE WORLD", 1995-present

MARQUIS "WHO IS WHO IN MEDICINE AND HEALTHCARE", 2004-present

Full-Time Active Member, the New York Academy of Sciences, 2006

More than 500 citations in scientific literature

Ad hoc member of NIAID study section:

"Bacteriology and Mycology 1", 1999-2001

Ad hoc reviewer for Department of Veterans Affairs:

Office of External Reviews, 2000-present

Ad hoc reviewer for University of Missouri Research Board:

GRANT APPLICATION SYSTEM, 2004-present

Ad hoc reviewer for peer-view scientific journals:

Infection and Immunity, Washington, DC, USA, 1993-present

Journal of Endotoxin Research, Cambridge, MA, USA, 1994-present

European Journal of Biochemistry, Zurich, Switzerland, 1995-present

FEMS Immunology and Medical Microbiology, 1998-present

Journal of Immunology, Danville, NJ, USA, 1996-present

VII. UNDERGRADUATE MENTORING AND GRADUATE THESIS ADVISOR

Master Thesis:

1983-1984 Yachmenev S. "Chromatographic characterization of activated form of glucocorticoid-receptor complexes in heart cytosol", All-Union Cardiology Research Center, Moscow, USSR

1983-1984 Petrichenko I. "Inter-conversion of activated and non-activated forms of glucocorticoid-receptor complexes: role of nonspecific inhibitors of phosphatases", All-Union Cardiology Research Center, Moscow, USSR

Ph.D. Thesis:

1986-1989 Bocharov A. "Bioartificial liver support system based on hepatocytes culturing on microcarriers", All-Union Cardiology Research Center, Moscow, USSR

Postdoctoral fellows supervised:

1993-1995 Yachmenev S, Ph.D., Department of Emergency and Critical Care Medicine, Faculty of Medicine, United Arab Emirates University, Al Ain, U.A.E.

1996-1998 Alipio A, Ph.D., KU Medical Center, Kansas City, KS

2001-2004 Norkin M, MD and PhD, UMKC School of Medicine, Kansas City, MO

2000-2005 Zoubine M, PhD, UMKC School of Medicine

VIII. ADMINISTRATION:

Director of Research Laboratory, Department of Emergency and Critical Care Medicine, Faculty of Medicine, United Arab Emirates University, Al Ain, United Arab Emirates.

Chairman, Institutional Animal Care and Use Committee, UMKC, Kansas City, MO

Director, Laboratory of Macrophage Biology, UMKC School of Medicine

IX. RESEARCH ACTIVITIES:

1. Brief statement of research interest:

Tumor microenvironment has a strong impact on immune surveillance and effector properties of macrophages (Mϕ). Mϕ recruited to tumors, a.k.a. tumor-associated Mϕ (TAMs), show M2-like phenotype of alternatively-activated cells (IL-12^{low}, IL-23^{low}, and IL-10^{high}) that is believed to promote tumor growth and metastasis. Therefore, immunotherapies aimed at the switching M1/M2 balance towards M1 classically activated Mϕ (IL-12^{high}, IL-23^{high}, and IL-10^{low}) represent a valid strategy for the development of novel immuno-modulatory approaches for treatment of cancer patients. Various tumor-derived constituents may contribute to the immunosuppressive microenvironment of solid tumors including anti-inflammatory cytokines, apoptotic bodies, prostaglandin E_2 (PGE_2), angiotensin II (Ang II) and others. In this regard, several experimental avenues are explored in my lab in the context of immuno-modulation and reprogramming of TAMs. The extraordinary intricacy of PGE_2 effects in Mϕ is complicated by multiple subtypes ($EP_{1\text{-}4}$) of PGE_2 receptor often co-expressed and operated in the same cell. In order to study the immuno-suppressive mechanisms of PGE_2 in TAMs, we generated EP_2^{low} and EP_4^{low} subclones of human THP-1 cells stably transfected with shRNA lentiviral vector plasmids capable of effective inhibition of EP_2 and EP_4, respectively. In addition, THP-1 cells were stably transfected with an NF-κB/AP-1-inducible reporter gene. Next, we developed an in vitro model reproducing tumor microenvironment and generating TAMs by co-culturing PMA-treated THP-1 cells (human Mϕ) with PGE2–

and Ang II–producing HCA-7 human carcinoma cells. Our data strongly indicate that tumor-derived PGE_2 may suppress M1 inflammatory response in TAMs in an EP_2-dependent manner suggesting potential efficacy of selective EP_2 antagonists in treatment of Cox-2^+ tumors. In addition, we studied PGE_2-controlled mechanisms of expression of various Toll-like receptors (TLRs) in, and TLR-dependent activation of, TAMs. Our results suggest that tumor-derived PGE_2 may inhibit expression of TLRs in EP_2-dependent manner, whereas EP_4-signaling pathway may increase expression and functional activity of TLRs in TAMs. Furthermore, using selective agonists and antagonist of AT_1 and AT_2 receptors for Ang II we found that Ang II may well be involved in the immuno-suppressive tumor microenvironment suggesting potential utility of Ang II receptor blockers for immunotherapy of Ang II-producing forms of cancer. Finally, we showed that targeted antagomir-mediated inhibition of miR21 and miR155 in THP-1 Mϕ may shift the M1/M2 balance and thus potentiate anti-cancer activities of TAMs.

2. Grants:

LPS-DIRECTED MACROPHAGE INNATE RESPONSES TO INFECTIONS

Role:	PI
Funding Agency:	NIH, NIAID
Grant period:	04/01/00-03/31/05
Total cost:	US $1,142,628

CLONNING OF NR2B SUBUNIT OF *N*-METHYL-D-ASPARTATE RECEPTOR

Role:	PI
Funding Agency:	NY GenTech, Unrestricted Grant
Grant period:	01/01/01-12/31/05
Total cost:	US $200,000

X. PUBLICATIONS (more than 500 citations in scientific literature)

Peer-reviewed papers:

Seleznev Yu.M., S.M. Danilov, S.P. Preobrazhensky, N.G. Volkova, **A. A. Shnyra**, G.V. Kolpakova, V.N. Smirnov, 1981. Evidence of the presence of glucocorticoid receptors in heart. Biochimija (Russian) 46: 162

Seleznev Yu.M., **A.A. Shnyra**, N.G. Volkova, V.N. Smirnov, R. Djozdjevic-Markovic, N, Lan and J.D. Baxter. 1981. Chromatographic studies on interconversions of "nonactivated" and "activated" forms of glucocorticoid-receptor complexes from rat heart cytosol. J. Steroid Biochem. 15: 155

Seleznev Yu. M., **A.A. Shnyra** and L.A. Medvedeva. 1984. New functions for the components of glucocorticoid receptor apparatus? Febs Letters 171:121

Seleznev Yu.M. and **A.A. Shnyra**. 1985. A factor modifying interaction of steroids with glucocorticoid receptors. Biochimija (Russian) 50:17

Idelson G.L., V.R. Muzykantov, E. Ye. Chekneva, **A.A. Shnyra**, B.V. Shekhonin, S.P. Domogatsky. 1987. *In vivo* administration of antibodies against type I collagen in rat: specific accumulation in spleen. Collagen Rel. Res. 7:383.

Sinitsyn V.V., A.G. Mamontova, E. Ye. Chekneva, **A.A. Shnyra**, S.P. Domogatsky. 1989. Rapid blood clearance of biotinylated IgG after infusion of avidin. J. Nucl. Med. 30:66

Vishnyakova T.G., **A.A. Shnyra**, A. V. Bocharov, V.G. Spirov, O.V. Smirnova, V.B. Rozen. 1989. Estimation of a direct regulatory effect of Estrogen on culturing hepatocytes tested by the changes in the unusual estrogen-binding protein level. Biochimija (Russian) 54:694

Rumjantsev A.G., B.M. Blochin, A.L. Tabachnik and **A.A. Shnyra**. 1989. Clinical efficiency of donor plasma with high titer of antibodies to endotoxin. Therapevtichesky Archive (Russian) 61:123

Smirnova O.V., T.G. Vishnyakova, V.B. Rozen, **A.A. Shnyra**, A.V. Bocharov and V.G. Spirov. 1990. *In vivo* and *in vitro* estimations of the direct effects of Estrogen on rat hepatocytes tested by the changes in the unusual estrogen-binding protein content. J. Steroid. Biochem. 35:457

Shnyra A., A. Bocharov, N. Bochkova and V. Spirov. 1990. Large-scale production and cultivation of hepatocytes on Biosilon microcarriers. Artif. Organs 14:421

Shnyra A., A. Bocharov, N. Bochkova and V. Spirov. 1991. Bioartificial liver using hepatocytes on Biosilon microcarriers: treatment of chemically-induced acute hepatic failure in rats. Artif. Organs 15:169

Nnalue N.A., **A. Shnyra**, K. Hultenby and A.A. Lindberg. 1992. *Salmonella choleraesuis* and *Salmonella typhimurium* associated with liver cells after intravenous inoculation of rats are localized mainly in Kupffer cells and multiply intracellularly. Infect. Immun. 60:2758

Shnyra A, K. Hultenby and A. A. Lindberg. 1993. Role of the physical state of *Salmonella* lipopolysaccharide in expression of biological and endotoxic properties. Infect. Immun. 61:5351

Shnyra A, and A. A. Lindberg.1995. Scavenger receptor pathway for lipopolysaccharide binding to Kupffer and endothelial liver cells *in vitro*. Infect. Immun. 63:865

Shnyra A. A., R. Brewington, A. Alipio, C. Amura, and D.C. Morrison. 1998. Reprogramming of LPS-primed macrophages is controlled by a counterbalanced production of IL-10 and IL-12. J. Immun. 160: 3729-3736

Brewington R., M. Chatterji, M. Zoubine, R. N. Miranda, M. Norimatsu, and **A. Shnyra**. 2001. IFN-γ-Independent Autocrine Cytokine Regulatory Mechanism in Reprogramming of Macrophage Responses to Bacterial Lipopolysaccharide. J. Immunol 167: 392–398.

Bedick J.C., **A. Shnyra**, D.W. Stanley, and R.L. Pardy 2001. Innate Immune reactions stimulated by a lipopolysaccharide-like component of the alga *Prototheca* (strain 289). 2001. Naturwissenschaften vol. 88 (11): 482-485

Malyshev I. Yu., **A. Shnyra**. 2003. Controlled modulation of inflammatory, stress, and apoptotic responses in macrophages. Curr Drug Targets Immune Endocr Metabol Disord 3(1):1-22.

Kamal R, Molteni A, Zoubine M, Norkin M, Reppert S, Xue Yu, Baybutt R, Herndon BLR, **Shnyra A**. 2004. Retinoic Acid-High Diet Controls M1/M2 Activation Phenotypes in Macrophages and Protects from Monocrotaline-Induced Pulmonary Fibrosis. Nutrition Research vol. 24(10): pp 773-785

Mehta A, Brewington R, Chatterji M, Zoubine M, Kinasewitz GT, Peer GT, Chang ACK, Taylor FB, **Shnyra A**. 2004. Infection-induced modulation of M1 and M2 phenotypes in circulating monocytes: role in immune monitoring and early prognosis of sepsis. Shock vol. 22(5): pp. 423-430.

Osorio I, **Shnyra A**, Santacruz K, Brewington R, Morrison D. 2006. Rasmussen's encephalitis: Interleukin-10-dependent Tc2 cell polarization may explain its pathophysiology and clinical course. Epilepsy Behav. 2007 Feb;10(1):206-11.

Badr M, **Shnyra A**, Zoubine M, Norkin M, Herndon B, Quinn T, Miranda R, Cunningham ML, and Molteni A. 2007. Phthalate-Induced Liver Protection Against Deleterious Effects of Th1 responses: A Potentially Serious Health Hazard? PPAR Research. Open Access Journal – Article ID 49671.

DeWitt JC, **Shnyra A**, Badr MZ, Loveless SE, Hoban D, Frame SR, Cunard R, Anderson SE, Meade BJ, Peden-Adams MM, Luebke RW, and Luster MI. 2008. Immunotoxicity of PFOA and other putative PPARα ligands. Critical Reviews in Toxicology Crit Rev Toxicol. 2008 Oct 2:1.

Surgucheva I, Weisman AD, Goldberg JL, **Shnyra A**, Surguchov A. Gamma-synuclein as a marker of retinal ganglion cells. Mol Vis. 2008 Aug 22;14:1540-8.

Wang Y, **Shnyra A**, Africa C, Warholic C, McArthur C. Activation of the extrinsic apoptotic pathway by TNF-alpha in human salivary gland (HSG) cells in vitro, suggests a role for the TNF receptor (TNF-R) and intercellular adhesion molecule-1 (ICAM-1) in Sjögren's syndrome-associated autoimmune sialadenitis. Arch Oral Biol. 2009 Nov;54(11):986-96.

Books and Book Chapters:

Shnyra A. A., and Yu. M. Seleznev. 1983. Specific factor for the glucocorticoid-receptor interaction. In*: Metabolism, structure and function of myocardial cells*. Second All-Union Symposium. Ed.: V.N. Smirnov. Medicine, Tashkent, p. 17

Shnyra A.A., G.F. Kalantarov, T.V. Vlasik, I.N. Trakht, A. Yu. Mayatnikov, A.L. Tabachnik, D.V. Borovikov and V.L. Golubych. 1990. Monoclonal antibody to lipid A prevents the development of haemodynamic disorders in endotoxemia. In*: Advances in Experimental Medicine and Biology*. vol. 256. Endotoxin. Eds.: Friedman H., T.W. Klein, M. Nakano and A. Nowotny. Plenum Press, New York, p. 681

Shnyra A.A., N. Hirohashi, M.-G. Lei, J. Ware and D.C. Morrison. 1995. LPS-dependent, CD14-independent scavenger receptor activation pathway for pro-inflammatory cytokine responses in rat Kupffer cells and endothelial liver cells. In: *The Immune Consequences of Trauma, Shock and Sepsis. Mechanisms and*

Therapeutic Approaches, vol. I. Eds.: E. Faist, A. E. Baue, F. W. Schildberg. Pabst Science Publishers, Lengerich, 1996, p.839.

Alipio A. E., D. C. Morrison, and **A. A. Shnyra**. Selective Immuno-regulatory Cytokines Reproduce Low Dose LPS reprogramming of Mouse Macrophages. In: *The Immune Consequences of Trauma*, *Shock and Sepsis. Mechanisms and Therapeutic Approaches*, vol. II. Ed.: E. Faist. Monduzzi Editore, 1997, Bologna, Italy, p. 321

Shnyra A.A., S. Yachmenev, J. Ware, A.-K. Persson, T. Midtvedt, D.C. Morrison. "Mechanism of LPS-induced activation in Kupffer cells: potential regulatory role of gut-derived endotoxin". In: *Proceedings of the 8-th International symposium on cells of the hepatic sinusoids.* Eds.: E. Wisse, D. L. Knook and C. Balabaud. Kupffer cell foundation.1998. Bordeaux, France

Shnyra A. A. LPS and scavenger receptors. In: *Endotoxin in Health and Disease*. Eds.: D. C. Morrison, H. Brade, S. Opal, and S. Vogel. Marcel Dekker Inc., New York, NY, 1999, pp. 437-448.

D.C. Morrison, R. Silverstein, M. Luchi, and **Shnyra A**. Recent Findings About Structure, Function and Relationships of Bacterial Endotoxins. Ed.: S.M. Opal and A. Cross. In: Infectious Disease Clinics of North America. W.B. Sunders Company, Philadelphia, PE, 1999, 313-340.

Shnyra A., M. Luchi, J.J. Gao, C. Papasian, D. Horn, R. Silverstein, M. Luchi, and D.C. Morrison. Endotoxin in Human Disease and Its Endogenous Control. Ed. Eu. Faist, and F. Fry. In: Multiple Organ Failure. Springer-Verlag New York Inc., New York, NJ, USA, 1999.

Luchi, M., D.C. Morrison and **Shnyra A.** Preparation and Analysis of Endotoxin from Pathogenic Bacteria. In: Septic Shock Methods and Protocols. Ed.: T.J. Evans. The Humana Press Inc., 2000, pp. 13-25.

Recent presentations at International and National Meetings:

Brandy M. Conner, Julia Ahn, Edith Chang, and Alex **Shnyra**. PROSTAGLANDIN E2-DEPENDENT MODULATION OF MACROPHAGES' RESPONSES BY COLON CANCER CELLS. Proceedings of the Tri-Society Annual Conference, PP1-005, p. 27, Lisbon, October 18-21, 2009.

A.K. Rutatangwa, R. Bean, N.J. Zarkadis, A.R. Streit, A. **Shnyra**. E01. Distinct role of PGE2 receptor subtypes in immunoediting of tumor-associated macrophages. Annals of Oncology 22 (Supplement 3): iii35, 2011.
NJ. Zarkadis, A.K. Rutatangwa, R. Bean, A.R. Streit, A. **Shnyra**. Does PGE2 control the M1/M2 paradigm in tumor-associated macrophages? Annals of Oncology 22 (Supplement 3): iii35, 2011.

A.R. Streit, A.K. Rutatangwa, N.J. Zarkadis, R. Bean, A. **Shnyra**. PGE2 may regulate expression of Toll-like receptors in tumor-associated macrophages. Annals of Oncology 22 (Supplement 3): iii35, 2011.

R. Bean, A.K. Rutatangwa, N.J. Zarkadis, A.R. Streit, A. **Shnyra**. MicroRNA expression profiles for M1, M2, and tumor-associated macrophages (TAMs) indicate a possible mechanism for TAMs reprogramming. Annals of Oncology 22 (Supplement 3): iii35, 2011.

Gromov* D, Ratatangwa* A, Demaree D, Lee M, Calka B, Bean R., and **Shnyra A**. Role of PGE_2 in Immuno-Editing of Tumor-Associated Macrophages. Annual Meeting of the Society for Leukocyte Biology, October 2012.

Lee M, Demaree D, Bean R, Gromov D, Calka B, and **A. Shnyra**. DOES miRNA98 REGULATE ANTI-TUMOR ACTIVITIES OF MACROPHAGES? Annual Meeting of the Society for Leukocyte Biology, October 2012.

XI. PERSONAL DATA:

DATE OF BIRTH:	January 5, 1956
PLACE OF BIRTH:	Kamchatka, Russia
CITIZENSHIP:	USA
MARITAL STATUS:	Married to Irina Shnyra, M.D. Children: Ksenia 01.13.81; Olga 05.17.84; Anton 04.16.87
HOME ADDRESS:	12127 Goodman Street Overland Park, KS 66213 Tel.: # (913) 663-1791
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XII. PROFESSIONAL REFERENCES

1. Prof. Christopher Papasian
Chair

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UMKC School of Medicine
2411 Holmes Street
Kansas City, MO 64108
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2. Prof. TED L. PARDY

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3. Prof. GLORIA E. MEREDITH
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Rosalind Franklin University
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4. Prof. BARRY FESTOFF
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5. PROF. AGOSTINO MOLTENI
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6. PROF. MAHMOUD S. AHMED
Director

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