BIOGRAPHICAL SKETCH

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NAME: OKSANA B SEREBRENNIKOVA

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

POSITION TITLE: Laboratory manager/Scientist, IT Bio, LLC

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
Saratov State University (Saratov, Russia)	BS/MS	06/1995	Biology
Institute of Biochemistry & Physiology of Plants & Microorganisms (Saratov, Russia)	PhD	07/1998	Microbiology
Thomas Jefferson University (Philadelphia, USA)	Postdoctoral	2001-2002	Signal transduction
Tufts Medical Center (Boston, USA)	Postdoctoral	2002-2012	Cancer Research
Tufts Medical Center (Boston, USA)	Postdoctoral	2013-2018	Molecular Biology

A. Personal Statement

I am a resourceful scientist with substantial post-doctoral research experience in immunology, cancer research, molecular and cell biology. I have motivation, leadership, training, and expertise necessary to successfully carry out the proposed research project. My extensive experience with mammalian cell culture (cancer cell lines, primary cells, and stable cell line development), cellular assays (viability, flow cytometry, reporter assays), variety of molecular biology techniques (RNA/DNA isolation and manipulation, cloning and mutagenesis, RT-PCR and qPCR, siRNA/shRNA, transfection and viral transduction) and biochemical techniques (protein extraction and cell fractionation, Western blotting, immunoprecipitation, ELISA) will be a valuable asset for this work.

The focus of my research is immunology and cancer. I studied the role of MAP3K8 in intestinal inflammation and tumorigenesis in $Apc^{Min/+}$ mouse model of colon cancer. Over the past 10 years I have worked with different mouse models (LPS-induced septic shock mouse model, Foxp3-GFP mouse, mouse cancer models), maintained mouse transgenic colony (breeding, weaning, tagging, genotyping), performed injections (intraperitoneal, intravenous, and subcutaneous, regulatory T-cell injection), and bone marrow transplantations, animal tissue harvest, fixation, IHC, and RNA/DNA isolation. In addition, I successfully collaborated with other researchers, managed mouse colony and lab, and trained and supervised lab personal. As a result, I am aware of the importance of realistic research plan, timeline, budget and communication among project members. The current application builds logically on my prior work and experience.

B. Positions and Honors

Positions and Employment

1994-2001	Technician/ Post-graduate Student/ Staff Scientist, Institute of Biochemistry & Physiology of Plants & Microorganisms, Saratov, Russia
1999	Visiting Fellow, University of Milan, Milan, Italy
2001-2002	Postdoctoral Fellow, Thomas Jefferson University, Philadelphia, PA
2002-2012	Postdoctoral Fellow, Tufts Medical Center, Boston, MA
2013-2018	Postdoctoral Fellow, Tufts Medical Center, Boston, MA
2018-current	Scientist/Manager, IT Bio LLC, Boston, MA

Honors

2001 INTAS Fellowship grant for Young Scientists, Fellowship Reference # YSF 00-160
1999 FEMS Fellowship, Delft, The Netherlands
1999 UNESCO Fellowship, Paris, France
1998 Personal Grant # HBA80318, Open Sci. Inst. Assistance Foundation, Moscow, Russia
1995 Personal Post-graduate Student Grant, International Science Foundation, New York, USA
1994 Personal Student Grant, International Science Foundation, New York, USA

C. Contributions to Science

1. Protective role of MAP3K8 in intestinal tumorigenesis.

The *Tpl2* protooncogene is a MAP3 kinase that plays an important role in cancer. Elevated Tpl2 activity was demonstrated in a number of human cancers including breast cancer, colon cancer, endometrial cancer, gastric cancer, nasopharyngeal carcinoma, thymoma, lymphoma, and EBV-related Hodgkin's lymphoma. Upregulation of Tpl2 in various tumor types strongly indicates its association with tumorigenesis and/or cancer progression. Genetic susceptibility to colorectal carcinogenesis has been linked to a host of germ-line mutations that give rise either to familial adenomatous polyposis (FAP) or to hereditary nonpolyposis colorectal cancer. FAP is caused by germ-line mutations of the *APC* gene and is characterized by the development of large numbers of intestinal polyps early in life. Some of these polyps ultimately progress to give rise to malignant colorectal tumors. *M*utations in *APC gene* are also detected in sporadic tumors and accounted for at least 95% of human malignant colorectal tumors. Germ-line mutations of the *APC* gene in mice (*Apc^{min}* mice) give rise to a syndrome that is similar to the FAP syndrome in humans.

In our study we demonstrated that Tpl2 plaid protective role in *Apc^{min}*-induced intestinal tumorigenesis. Bone marrow transplantation experiments revealed that the increased susceptibility of Apc$^{min/+}$/Tpl2$^{-/-}$ mice to intestinal tumorigenesis is partially driven by hematopoietic cells. The ablation of *Tpl2* in Apc$^{min/+}$ mice was shown to promote the establishment of a proinflammatory environment that stimulates oncogenesis in the intestinal mucosa. The earliest events in the sequence that leads to inflammation and tumorigenesis appeared to be the secretion of IL-10 and the generation of inducible Tregs (iTregs), both of which were impaired in Tpl2$^{-/-}$ mice. The low levels of IL-10 and the low number and functional impairment of Tregs promote inflammation and tumorigenesis in the context of the *Apc^{min}* mutation. In contrast with the strong evidence associated with the oncogenic roles of Tpl2, we demonstrated that under certain conditions, Tpl2 may serve tumor suppressive roles.

Tpl2-targeting agents could be effective therapeutic strategies for many types of inflammatory disease and may also provide novel insights into potential anti-cancer therapeutics strategies in several cancers in which Tpl2 plays an important role as a tumor promoting gene. Although small molecule inhibitors exist for the targeting of the Tpl2-MEK-ERK pathway, side effects could be a serious issue. Unfortunately, the role of Tpl2 in tumorigenesis is complex, as either over-expression or reduced-expression can promote tumor formation depending on the cancer type. As a result, due to the probability of secondary malignancies by Tpl2 targeting, clinical application of Tpl2 as a novel therapeutic target for advanced cancer patients needs to be further validated.

1. Serebrennikova OB, Tsatsanis C, Mao C, Gounaris E, Ren W, Siracusa LD, Eliopoulos AG, Khazaie K, Tsichlis PN. (2012) Tpl2 ablation promotes intestinal inflammation and tumorigenesis in Apcmin mice by inhibiting IL-10 secretion and regulatory T-cell generation, *Proc. Natl. Acad. Sci. U S A* May 1;109(18):E1082-91.
2. Serebrennikova, O., Naber, S., Tsichlis, P. (2004) Tpl2 ablation accelerates tumorigenesis in Apcmin mice, Abstract at Tufts-NEMC Research Day, March 2004, Boston MA (poster presentation).

2. Role of Tpl2 in TNFa-induced apoptosis.

Cancer is second only to heart disease as the leading cause of death in industrialized countries. Although mortality rates have declined in recent years due to earlier detection and more options in treatment, the outlook for certain cancers remains bleak. Conventional cancer chemotherapeutics have a small therapeutic index between cancer and normal cells. Complicating matters further is the almost inevitable onset of resistance and subsequent relapse. In recent years, the focus has shifted to less-toxic therapeutics that target specific signaling pathways driving inappropriate cell growth and proliferation. In addition to aberrant growth signals, many cancers also have dysfunction in the ability to undergo apoptosis. Overexpression of antiapoptotic genes have been correlated with tumorigenesis and resistance to chemotherapy. An alternative

approach to the treatment of cancer, therefore, would be to reestablish the cell death program and set conditions such that cells can undergo apoptosis given an appropriate stimulus.
Tumor necrosis factor (TNF) is a multifunctional cytokine that plays important roles in diverse cellular events including cell survival and cell death. With regard to cancer, TNF is a double-dealer. it could stimulate tumor growth and it could be a cancer killer. The property of TNF in inducing cancer cell death renders it a potential cancer therapeutic.
TNF is a major activator of Tpl2 and in the tumor microenvironment it is produced by inflammatory cells as well as cancer cells. In the current work we demonstrated that Tpl2 protects carcinoma cell from TNF-induced apoptosis through the regulation of Caspase 8 activity and mitochondrial pathway of apoptosis. The knockdown of Tpl2, in combination with TNF, causes synthetic lethality in human carcinoma cell lines by downregulation of antiapoptotic protein MCL1 and Caspase inhibitor FLIP, and by upregulating Caspase 8 levels through microRNA 21.
These findings demonstrate a novel mechanism of regulation of TNF-induced apoptosis and can potentially offer a specific and relatively nontoxic treatment of certain type of cancer. These results are currently being prepared for the publication and we continue working on the mechanisms of cancer cell resistance to TNF.

1. Serebrennikova OB, Paraskevopoulou MD, Aguado-Fraile E, Taraslia V, Ren W, Thapa G, Roper J, Du K, Tsichlis PN. The combination of *TPL2* knockdown and TNFα causes synthetic lethality in human carcinoma cell lines (paper submitted)
2. Serebrennikova OB, Tsichlis PN Tpl2 regulates TNFα-induced caspase-8 activation and apoptosis (work in progress)

3. In addition to the contributions described above, where I was a main researcher, I also participated in multiple collaborative studies. We investigated the role of Tpl2 in calcium signaling and migration, and demonstrated the association between microRNA214 and colitis and colitis-associated cancer. With a team of collaborators, we also studied the role of epigenetic regulator KDM2B in fibroblast immortalization and breast cancer. My contribution was not limited only to basic research. in addition, I analyzed clinical samples for the Metformin phase I clinical trial where we evaluated the safety of combining Metformin with anticancer chemotherapy.

1. Polytarchou C, Hommes DW, Palumbo T, Hatziapostolou M, Koutsioumpa M, Koukos G, van der Meulen-de Jong AE, Oikonomopoulos A, van Deen WK, Vorvis C, Serebrennikova OB, Birli E, Choi J, Chang L, Anton PA, Tsichlis PN, Pothoulakis C, Verspaget HW, Iliopoulos D. (2015) MicroRNA214 is associated with progression of ulcerative colitis, and inhibition reduces development of colitis and colitis-associated cancer in mice. *Gastroenterology* Oct; 149(4): 981-92
2. Hatziapostolou M, Koukos G, Polytarchou C, Kottakis F, Serebrennikova O, Kuliopulos A, Tsichlis PN. (2011) Tumor progression locus 2 mediates signal-induced increases in cytoplasmic calcium and cell migration*, Sci Signal* Aug 23; 4(187): ra55
3. Pfau R, Tzatsos A, Kampranis S, Serebrennikova OB, Bear S, Tsichlis P. (2008) Members of a family of JmjC domain-containing oncoproteins immortalize embryonic fibroblasts via a JmjC domain-dependent process, *Proc Natl Acad Sci U S A* Feb 12; 105(6): 1907-12
4. Metformin phase I clinical trial “Prospective evaluation of clinical safety of combining metformin with anticancer chemotherapy”, IRB# 10026, Tufts Medical Center, Boston 2011-2017

D. Additional Information: Research Support and/or Scholastic Performance

Completed Research Support

R01CA186729 (Tsichlis) 04/15/15-03/31/20
Differential regulation of RNA processing by Akt isoforms
Specific Aims: 1) To determine the role of IWS1-dependent RNA processing in human lung Cancer; 2) To determine how IWS1 phosphorylation controls RNA processing; 3) To determine the biological consequences of the Akt-dependent phosphorylation of other proteins involved in RNA splicing.
Role: Post-Doctoral Fellow

NCI/NIH 1R43CA244048 (Junghans) 09/01/2019-08/31/2020
Co-targeting Ezh2 with PD1 to improve T cell exhaustion reversal and tumor responses
The major goals of this project are to test the synergistic benefit of co-applying checkpoint receptor therapy with Ezh2 inhibitors for antitumor responses in mouse models.
Role: Investigator