BIOGRAPHICAL SKETCH

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NAME: Scotto, Kathleen W.

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

POSITION TITLE: Professor of Pharmacology

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
St. John's University, Jamaica, NY	B.S.	05/1977	Biology
Cornell University, Sloan-Kettering Division, NY, NY	Ph.D.	05/1983	Molecular Biology
Sloan-Kettering Institute, NY, NY	Postdoctoral	03/1984	
The Rockefeller University, NY, NY	Postdoctoral	11/1988	

A. Personal Statement

I am a cancer researcher, with a long-term focus on the regulation of genes involved in cellular sensitivity to drug and radiation treatment. Specifically, my research, largely supported over the years by funding from the NIH-NCI, has focused on transcriptional regulation of ABC transporters; more recently, we have identified a novel role for one of these transporters in the regulation of autophagy, opening a new area of investigation for this class of proteins. We also study the role of membrane transporters in regulation of cancer metabolism.

My commitment to the training and mentoring of the next generation of scientists began when I was a faculty member at the Weill Cornell Graduate School of Medical Sciences and has extended throughout my career, leading to my current role(s) as Vice Chancellor for Research and Research Training for Rutgers Biomedical and Health Sciences, Vice Dean of the Rutgers School of Graduate Studies (SGS) and Unit Dean of the SGS-Biomedical Health Sciences division. My commitment has taken many forms over the years – as an NIH-funded researcher, I have trained dozens of undergraduate, graduate and postdoctoral scientists. At a local level, I was the chair of the Research and Development Council of New Jersey when we received approval for the Governor's STEM scholars program, a public-private partnership that brings together a diverse and representative group of high school and post-secondary student leaders who are interested in pursuing a STEM- related career. As long-term chair of the American Association for Cancer Research Science Education and Career Development Committee, I have been an advocate for, and participant in, the training of high school and undergraduate students interested in research careers. The recognized success of this committee has recently led AACR to expand its mandate to include graduate, postgraduate and junior faculty members on both sides of the clinical research spectrum to foster the young scientists who will make up the force translating across the research continuum in the future.

I was delighted to be asked to join the Advisory Board for the T32 Post-doctoral Training Program in Genetics and Computational Genomics of Cancer (GCGC) at the Rutgers Cancer Institute of New Jersey (RCINJ). As a cancer researcher with administrative role(s) that allow me to work across multiple scientific disciplines and schools, I am uniquely positioned to identify the critical individuals/components within Rutgers that will allow us to enhance an already top quality infrastructure to train new translational cancer researchers. Moreover, as Program Director for our CTSA TL1, I am strongly invested in creating the optimal infrastructure for the training of the translational researchers of the future.

Ongoing and recently completed projects that I would like to highlight include:

NIH/NCATS
CTSA (Parent) Panetteiri (PI) 03/11/19 – 03/10/24

CTSA TL1 (Training) **Scotto** (PI)
This CTSA Institutional Training Core (TL1) has been designed to leverage the strengths of The **New Jersey Alliance for Clinical and Translational Science (NJ ACTS**), the umbrella organization that will provide an infrastructure to support and enhance clinical and translational research and training in New Jersey. Led by Rutgers Biomedical and Health Sciences (RBHS) and administered by the Rutgers Institute for Translational Medicine and Science (RITMS), NJ-ACTS comprises an Alliance of three universities (Rutgers University, Princeton University, and the New Jersey Institute of Technology) together with community- based organizations, hospitals, community health centers, outpatient practices, data centers and two Health Information Exchanges. This unique and dynamic environment will allow us to create a robust and effective platform to train the next generation of translational researchers.

1R01CA226746-01 Sabaawy (PI) 07/02/2018 – 6/30/2023
NIH/NCI **Scotto** (co-I)
Mechanisms of targeting cellular self-renewal in glioblastoma.
The goals of this proposal are to delineate the role of BMI1 in glioblastoma tumor initiation and progression and develop BMI targeting therapies using patient derived models and genetically engineered mouse models.
Role: Co-Investigator

NSF Birnie (PI) 08/2017 – 07/2022
Scotto (co-I)
Rutgers University I-Corps Site for Entrepreneurship Acceleration
The proposed Rutgers University I-Corps Site is designed to cultivate a pool of early stage ideas and assist with bringing viable concepts through the commercialization pathway to the marketplace. These key elements are embodied in the Business Model Canvas that will be used in the Rutgers I-Corps program, along with targeted training and mentoring.
Role: Co-PI

B. Positions and Honors

Positions and Employment

1989-1996 Assistant Member, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, NY
1989-1996 Assistant Professor, Cornell University Graduate School of Medical Sciences, Department of Pharmacology, New York, NY
1996-2001 Associate Member, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, NY
1996-2001 Associate Professor, Cornell University Graduate School of Medical Sciences, Department of Pharmacology, New York, NY
1997-2001 Director, Graduate Program in Pharmacology, Cornell University, New York, NY
2001-2004 Member, Department of Pharmacology, Fox Chase Cancer Center, Philadelphia, PA
2001-2004 Adjunct Associate Professor, Cornell University Graduate School of Medical Sciences, Department of Pharmacology, New York, NY
2003-2004 Director, Translational Research Facility, FCCC
2004 Interim Leader, Program in Drug and Radiation Response,
FCCC 2004 Acting Chair, Department of Pharmacology, FCCC
2004- Professor of Pharmacology, Cancer Institute of New Jersey, Robert Wood Johnson School of Medicine, University of Medicine and Dentistry of New Jersey, New Brunswick, NJ
2004- Resident Member, Rutgers Cancer Institute of New Jersey, New Brunswick,
NJ 2004-2008 Senior Associate Dean of Research, RWJMS, UMDNJ
2005-2007 Interim Vice President of Research, UM
DNJ 2007-2013 Vice President of Research, UMDNJ
2007-2011 Interim Dean for the Graduate School of Biomedical Sciences,
UMDNJ 2011-2013 Dean for the Graduate School of Biomedical Sciences,
UMDNJ
2013- Vice Chancellor for Research and Research Training, Rutgers Biomedical and Health

Sciences, Rutgers, The State University of New Jersey, New Brunswick, NJ
2013-2017 Dean, Graduate School of Biomedical Sciences, Rutgers Biomedical and Health Sciences, Rutgers, The State University of New Jersey, New Brunswick, NJ
2017- Vice Dean, School of Graduate Studies, Rutgers, The State University of New Jersey, New Brunswick, NJ Rutgers, The State University of New Jersey, New Brunswick, NJ
2017 - Unit Dean, SGS-Biomedical and Health Sciences,

Other Experience and Professional Memberships

Member	American Association for Cancer Research (AACR)
Member	Women in Cancer Research (WICR)
Member	New York Academy of the Sciences (NYAS)
Vice Chair	Research and Development Council of New Jersey
Chair	Research and Development Council of New Jersey
Board Member	Commercialization Center for Innovative
Technologies- Board Member	Foundation Venture Capital Group
Board Liaison	BioNJ
Vice Chair	New Jersey Commission on Cancer Research (Legislative appointment)
Chair	AACR Science Education and Career Development Committee

Honors

1985-1986	ACS Postdoctoral Fellowship
1986-1988	NIH National Research Service
Award 1993-1994	Wendy Will Case Cancer Fund
Award	
2000-2001	The Byrne Award for Translational Research
2008	NJABR Outstanding Women in Research
Award	
2009	AACR: Outstanding Dedication to the Scientist Survivor Program Award
2011	Distinguished Alumna of the Year, Weill Cornell Graduate School of Medical
	Sciences, Cornell University

C. Contribution to Science

1. As a graduate student, I cloned the gene for the hamster ABC transporter P-glycoprotein (Pgp), and published the first description of this gene. My observation that P-glycoprotein was overexpressed at the level of RNA and protein in drug-selected cells without commensurate amplification of the Pgp gene was one of the first observations of a drug-selected increase in gene expression, leading to the hypothesis that Pgp overexpression in drug-resistant tumor cells was accomplished at the level of transcription. Following my graduate experience, I was a postdoc in the laboratory of Dr. Robert Roeder, where I studied the biochemistry of transcription and was the first to identify USF, previously identified as a regulator of the viral ML promoter, as an upstream activator of a eukaryotic gene.
   a. **Scotto KW**, Biedler JL, Melera PW. Amplification and expression of genes associated with multidrug resistance in mammalian cells. Science.1986 May 9;232(4751):751-5. PubMed PMID: 2421411.
   b. Biedler JL, Chang TD, **Scotto KW**, Melera PW, Spengler BA. Chromosomal organization of amplified genes in multidrug-resistant Chinese hamster cells. Cancer Res. 1988 Jun 1;48(11):3179-87. PubMed PMID:3365701.
   c. **Scotto KW**, Kaulen H, Roeder RG. Positive and negative regulation of the gene for transcription factor IIIA in Xenopus laevis oocytes. Genes Dev. 1989 May;3(5):651-62. PubMed PMID: 2744458.

2. During my early career at Memorial Sloan-Kettering Cancer Center, I pursued my interest in the regulation of drug resistance genes. My laboratory identified the transcriptional mechanism regulating overexpression of the hamster P-glycoprotein gene, identifying a novel element, MED1, which regulated selection of alternative transcription start sites. This was accomplished at a time when little was known about multiple transcription start sites, and almost nothing was known about their regulation.
   a. Ince TA, **Scotto KW**. Differential utilization of multiple transcription start points accompanies the

overexpression of the P-glycoprotein-encoding gene in Chinese hamster lung cells. Gene. 1995 Apr 24;156(2):287-90. PubMed PMID: 7758970.

b. Ince T A, **Scotto KW**. A conserved downstream element defines a new class of RNA polymerase II promoters. J Bioi Chem. 1995 Dec 22;270(51):30249-52. PubMed PMID: 8530439.

c. Ince TA, **Scotto KW**. Stable transfection of the P-glycoprotein promoter reproduces the endogenous overexpression phenotype: the role of MED-1. Cancer Res. 1996 May 1;56(9):2021-4. PubMed PMID: 8616844.

d. Lin Y, Ince T A, **Scotto KW**. Optimization of a versatile in vitro transcription assay for the expression of multiple start site TAT A-less promoters. Biochemistry. 2001 Oct 30;40(43):12959-66. PubMed PMID: 11669633.

3. My laboratory progressed from analysis of the hamster Pgp gene to studying the transcriptional regulation of the human Pgp gene, MDR1. The many contributions we made to the field include:
1) the first demonstration that the MDR1 gene could be rapidly activated by chemotherapeutics in a clinical setting; 2) the finding that p53 represses MDR1 transcription through a novel element that has since been identified in other p53-repressed promoters; 3) the identification of NF-Y and Sp1 as regulators of stress-induced MDR1 transcription; 4) the first report of epigenetic regulation of MDR1 by HDAC inhibitors, with identification of the factors mediating this regulation.

   a. Jin S, **Scotto K W**. Transcriptional regulation of the MDR1 gene by histone acetyltransferase and deacetylase is mediated by NF-Y. Mol Cell Bioi. 1998 Jul;18(7):4377-84. PubMed PMID: 9632821; PubMed Central PMCID: PMC109021.

   b. Abolhoda A, Wilson AE, Ross H, Danenberg PV, Burt M, **Scotto KW**. Rapid activation of MDR1 gene expression in human metastatic sarcoma after in vivo exposure to doxorubicin. Clin Cancer Res.1999 Nov;5(11):3352-6. PubMed PMID: 10589744.

   c. Hu Z, Jin S, **Scotto KW**. Transcriptional activation of the MDR1 gene by UV irradiation. Role of NF-Y and Sp1. J Bioi Chem. 2000 Jan 28;275(4):2979-85. PubMed PMID: 10644769.

   d. Johnson RA, Ince TA, **Scotto K W.** Transcriptional repression by p53 through direct binding to a novel DNA element. J Bioi Chem. 2001 Jul20;276(29):27716-20. PubMed PMID: 11350951.

4. Another major interest of the laboratory has been the discovery of new cancer therapeutics. Our laboratory was the first to show that ET-743 (trabectidin, Yondelis; licensed by J&J) has a unique mechanism of action, inhibiting induction of transcription without impacting constitutive transcription. Our studies provided the foundation for additional studies from other laboratories, and informed design of clinical studies of this novel agent. These studies also mark the beginning of a close collaboration with the Bertino laboratory in the search for novel cancer chemotherapeutics.

   a. Takahashi N, Li WW, Banerjee D, **Scotto KW**, Bertino JR. Sequence-dependent enhancement of

      cytotoxicity produced by ecteinascidin 743 (ET -743) with doxorubicin or paclitaxel in soft tissue sarcoma cells. Clin Cancer Res. 2001 Oct;7(10):3251-7. PubMed PMID: 11595721.

   b. **Scotto, KW**. ET-743: more than an innovative mechanism of action. Anticancer Drugs. 2002 May;13 Suppi1:S3-6. PubMedPMID:12173491.

   c. Friedman D, Hu Z, Kolb EA, Gorfajn B, **Scotto KW**. Ecteinascidin-743 inhibits activated but not constitutive transcription. Cancer Res. 2002 Jun 15;62(12):3377-81. PubMed PMID: 12067978.

   d. Takahashi N, Li W, Banerjee D, Guan Y, Wad a-Takahashi Y, Brennan MF, Chou TC, **Scotto KW**, Bertino JR. Sequence-dependent synergistic cytotoxicity of ecteinascidin-743 and paclitaxel in human breast cancer cell lines in vitro and in vivo. Cancer Res. 2002 Dec 1;62(23):6909-15. PubMed PMID: 12460906.

5. More recently, our laboratory has pursued two new areas of interest. We are now studying another ABC transporter, ABCG2, and have made two major discoveries: 1) ABCG2 expression can be downregulated by methylxanthines, identifying a new class of compounds with potential clinical relevance and 2) ABCG2 regulates autophagy in cancer cells. Current studies are testing the role of ABCG2 in autophagy regulation in vivo, and the implications for tumor survival, metastases and resistance to stress. A second area of interest is the regulation of alternative splicing in cancer. We have shown that methylxanthines regulate alternative splicing of -10% of the human genome. Using the tumor suppressor KLF6 as a model, we have identified splicing factors involved in this regulation and shown how these factors themselves are regulated

by a series of post-transcriptional mechanisms. Our current studies are aimed at identifying the signaling/metabolic pathways that are impacted by methylxanthines, and querying how dysfunction within those pathways could lead to aberrant and deleterious alternative transcripts in cancer cells.

a. Shi J, Hu Z, Pabon K, **Scotto KW**. Caffeine regulates alternative splicing in a subset of cancer-associated genes: a role for SC35. Mol Cell Biol. 2008 Jan;28(2):883-95. PubMed PMID: 18025108; PubMed Central PMCID:PMC2223418.
b. Ding R, Shi J, Pabon K, **Scotto KW**. Xanthines down-regulate the drug transporter ABCG2 and reverse multidrug resistance. Mol Pharmacol. 2012 Mar;81(3):328-37. PubMed PMID: 22113078; PubMed Central PMCID: PMC3286305.
c. Shi J, Pabon K, **Scotto KW**. Methylxanthines increase expression of the splicing factor SRSF2 by regulating multiple post-transcriptional mechanisms. J Biol Chem. 2015 Jun 12;290(24):14986-5003. PubMed PMID:25818199.
d. Ding, R., Jin S., Pabon, K., and **Scotto, KW**. A role for ABCG2 beyond drug transport: regulation of autophagy. Autophagy, 2016 May 3;12(5):737-51.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/pubmed/?term=scotto+k