BIOGRAPHICAL SKETCH

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NAME: Grossman, Steven Robert

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

POSITION TITLE: Professor of Internal Medicine and Human and Molecular Genetics

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
Princeton University, Princeton, NJ	AB	1984	Biology
University of Chicago, Chicago, IL	PhD	1989	Mol. Gen. & Cell Biology
University of Chicago, Chicago, IL	MD	1991	Medicine

A. Personal Statement

My longstanding interest has been to dissect the regulation of the p53 tumor suppressor network, and develop novel cancer therapeutic targets that lend cancer-cell specificity in tumors where the p53 network has been disrupted. My particular focus has been on factors that regulate p53 stability, such as ARF and MDM2, and our studies of ARF led us to a novel ARF-interacting transcription factor and potential oncotherapeutic target, C-terminal binding protein (CtBP). CtBP is a transcriptional coregulator that represses of multiple tumor suppressor genes, drives invasion/migration behavior and EMT in epithelial cells, is overexpressed and a poor prognostic factor in numerous common solid tumors, and is associated with drug resistance and self-renewal capacity of tumor initiating cells. Importantly, CtBP encodes a conserved and active dehydrogenase that regulates its transcriptional activities and senses cellular production of NADH which is increased in cancer cells.

My laboratory was the first to demonstrate the utility of the CtBP dehydrogenase as a therapeutic target in cancer, and since then, we have actively pursued the development of anti-CtBP therapeutics using structure-based approaches. Utilizing endogenous tumor models such as *Apc min* and pancreatic cancer cells knocked out for CtBP2 by CRISPR-Cas9, we have thoroughly validated CtBP2 as a key dependency for tumor growth. We continue to develop high affinity CtBP inhibitors as a novel class of anti-cancer therapeutic.

Our laboratory was also the first to identify factors that enhance the polyubiquitination and degradation of p53, extending the paradigm of known core regulators of p53 stability beyond MDM2. These “E4” factors include the p300 and CBP coactivators, which were previously known to function as acetyltrasferase (AT) coactivators of p53 in stress responses. We discovered that the AT and E4 functions of p300/CBP are spatially separated in the cell between nucleus and cytoplasm, explaining how these opposing regulatory functions exist in the same factors. In addition, we are intensively studying how p300/CBP and other coactivators, such as PCAF, contribute to p53 transactivation at different target genes by both regulating p53 and histone modifications at those promoter loci.

Our most recent work has focused on understanding the hyper-stability of mutant gain-of-function (GOF) p53 in lung cancer, and we have found that active DNA damage signaling pathways contribute to mutant p53 stability. We are actively pursuing therapeutic strategies to attack mutant p53 in lung cancer by modulating DNA damage signaling, as well as through novel protein metabolism strategies, which could then lead to destabilization and elimination of mutant p53 and inhibition of growth or apoptosis.

B. Positions and Honors

Positions and Employment

1991-1992 Intern in Medicine, Brigham and Women's Hospital
1992-1993 Junior Assistant Resident, Internal Medicine, Brigham and Women's Hospital
1993-1994 Postdoctoral Fellow, Laboratory of Dr Elliot Kieff, Brigham and Women's Hospital
1994-1997 Fellow in Medical Oncology, Dana-Farber Cancer Institute
1996-2002 Postdoctoral Fellow, Laboratory of Dr David Livingston, Dana-Farber Cancer Institute
1997-1999 Instructor in Medicine, Dana-Farber Cancer Institute
1997-2002 Associate Physician, Brigham and Women's Hospital
1998-2002 Staff Physician, Gastrointestinal Cancer Center, Dana-Farber Cancer Institute
1999-2002 Assistant Professor of Medicine (Developing), Harvard Medical School
2003-2008 Assistant Professor of Cancer Biology and Medicine, UMass Medical School
2004-2011 Staff Physician, Gastrointestinal Cancer Clinic, UMass Memorial Medical Center
2005-2011 Co-Director, Gastrointestinal Cancer Program, UMass Memorial Cancer Center
2008-2011 Associate Professor of Cancer Biology and Medicine, UMass Medical School
2010-2011 Medical Director, Simonds-Sinon Regional Cancer Center, Fitchburg, MA
2011-2013 Professor of Internal Medicine, Virginia Commonwealth University (VCU), Richmond, VA
2011-2020 Professor of Human and Molecular Genetics, VCU, Richmond, VA
2011-2020 Chair, Division of Hematology, Oncology, and Palliative Care, VCU, Richmond, VA
2011-2020 Staff Physician, GI Tumor Center, VCU Massey Cancer Center, Richmond, VA
2012-2020 Dianne Nunnally Hoppes Endowed Chair in Cancer Research, VCU, Richmond, VA
2013-2020 Professor of Internal Medicine (Tenured), VCU, Richmond, VA
2013-2020 Deputy Director, VCU Massey Cancer Center, Richmond, VA
2020- Professor of Medicine, Keck School of Medicine of USC, Los Angeles, CA
2020- Cancer Physician-in-Chief, USC Norris Comprehensive Cancer Center, Los Angeles, CA

Other Experience and Professional Memberships

1993- Massachusetts Medical Society
2006- American Society for Microbiology
2009-2016 TBG Grant Review Panel, American Cancer Society *(Ad hoc,* 2009-2012; Member 2012-2016)
2010-2015 NIH CAMP Study Section (*Ad hoc*, 2010; Member 2011-2015)
2012- American Society for Clinical Oncology
2013- American Association for Cancer Research
2014- American Society for Clinical Investigation
2015-2020 Board of Directors, Alliance for Clinical Trials in Oncology

Honors

1984 Summa Cum Laude
1984 Phi Beta Kappa
1984 Sigma Xi Research Society
1984 Medical Scientist Training Program
1991 Best Presentation, Senior Scientific Session, Pritzker School of Medicine
1993 Fellowship in Herpesvirus Research, National Foundation for Infectious Disease
1995 Postdoctoral Fellowship for Physicians, Howard Hughes Medical Institute
2000 New Investigator Award, Harcourt General Charitable Foundation
2001 Howard Temin Award, National Cancer Institute
2002 Kimmel Scholar Award, The Kimmel Foundation
2007 Excellence in Teaching Award, UMMS Department of Medicine
2012-2020 Dianne Nunnally Hoppes Endowed Chair in Cancer Research

C. Contribution to Science

1. **Understanding p53 turnover from polyubiquitination through proteasomal degradation-roles of E4 factors and proteasome adaptors.**
   The p53 tumor suppressor is a prototypically unstable protein, as the cell needs a ready supply of p53 mRNA, without active protein, to deal rapidly with oncogenic and other environmental stress. Stress, such as genotoxins, ionizing radiation, and metabolic changes rapidly stabilize p53 allowing

accumulation and activation, followed by resetting of the unstable phenotype once the stress has resolved. MDM2 is among the most critical E3 ubiquitin ligases governing p53 function, but can generally only monoubiquitinate, not polyubiquitinate, p53 at physiologic stoichiometries. My research has identified the p300/CBP histone acetylases as also serving as "E4" polyubiquitin ligases, facilitating cytoplasmic ubiquitin chain extension on p53 that targets it for proteasomal degradation. This finding, explains a prior conundrum surrounding regulation of p53 stability, explains why p53 is preferentially unstable in the cytoplasm, and provides a way forward for therapeutics that can stabilize wild type p53 in tumors, by guiding development of inhibitors of the p300/CBP E4 function. Further work in my lab demonstrated that delivery of polyubiquitinated p53 to the proteasome is regulated by adaptors, such as hHR23, and by MDM2 itself. My role has been to develop the initial ideas and experimental support for the E4 work as a post-doctoral fellow, followed by subsequent work in my own lab on the E4 and proteasome delivery aspects, also in collaboration with the Blattner lab. Current work is exploring how ubiquitination and proteasome adaptors regulate the transcription function of p53 on chromatin.

1. **Grossman SR**, Deato, MD, Brignone C, Chan HM, Kung AL, Tagami H, Nakatani Y, Livingston DM. A ubiquitin ligase activity of p300 cooperates with MDM2 to polyubiquitinate p53. Science 2003 300:342-344.
2. Kaur M, Pop M, Shi D, Brignone C, **Grossman SR**. hHR23B is required for genotoxic-specific activation of p53 and apoptosis. Oncogene 2007 26:1231-1237.
3. Shi D, Pop MS, Kulikov R, Love IM, Kung AL, **Grossman SR**. CBP and p300 are cytoplasmic E4 polyubiquitin ligases for p53. Proc Natl Acad Sci USA. 2009 106:16275-16280.
4. Akande OE, Damle PK, Pop M, Sherman NE, Szomju BB, Litovchick LV, **Grossman SR.** DBC1 regulates p53 stability via inhibition of CBP-dependent p53 polyubiquitination. Cell Rep 2019 26:3323-3335.

2. C-terminal binding protein (CtBP): a ubiquitous oncogene and dependency in multiple solid tumors

We identified CtBP2 in a screen for p19ARF interacting proteins investigating the mechanism of p53-independent tumor suppression by p19ARF. We subsequently found that ARF interacts with CtBP1 and 2, and promotes CtBP proteasomal degradation under conditions of cellular stress, leading to p53-independent apoptosis. Mechanistically, this was due to the abrogation of CtBP transcriptional repression of BIK and related BH3 proteins. We then showed that ARF also blocks CtBP-dependent migration/invasion activities, which are potently stimulated by hypoxia due to metabolic sensing by the CtBP dehydrogenase domain. CtBP regulation of migration/invasion was linked to both repression of PTEN, and also direct CtBP transactivation of the TIAM1 migration/metastasis gene (a rac/rho GEF), in CtBP's dual role as repressor and activator. Most recently, we have characterized CtBP as a true transforming oncogene in primary human and mouse cells, and have also shown that the *APC min* intestinal polyposis phenotype is suppressed by *Ctbp2* haploinsufficiency, "KPC" mice that develop pancreatic cancers live longer with fewer or no metastases after loss of one Ctbp2 allele, and the administration of 1st or 2nd generation CtBP inhibitors suppressed polyposis in Min mice and worked synergistically with chemotherapy to inhibit tumor growth in KPC mice. In ovarian cancer cells, CtBP was shown to repress DR4/5 death receptors, and thus shield high grade serous ovarian cancer cells from apoptosis through the extrinsic pathway. Our work has further demonstrated that CtBP's oncogenic actions in vivo are linked to its ability to drive a tumor initiating cell phenotype in both colon and pancreatic cancer.

1. Sumner ET, Chawla AT, Cororaton AD, Koblinski J, Kovi RC,Love IM, Szomju BB, Korwar S, Ellis KC, **Grossman SR**. Transforming activity and therapeutic targeting of C-terminal Binding Protein 2 in *Apc* mutated neoplasia. Oncogene 2017; 36:4810-4816.
2. Chawla AT, Cororaton AD, Idowu MO, Damle PK, Szomju B, Ellis KC, Patel BB, **Grossman SR**. An intestinal stem cell niche in *Apc* mutated neoplasia targetable by CtBP inhibition. Oncotarget 2018; 9:32408-32418.
3. Chawla AT, Chougoni KK, Joshi PJ, Cororaton AD, Memari P, Stansfield JC, Park H, Seth R, Szomju B, Sima AP, Idowu MO, Ellis KC, **Grossman SR**. CtBP- a targetable dependency for tumor initiating cell activity and metastasis in pancreatic adenocarcinoma. Oncogenesis 2019; 8:55.

4. Ding B, Yuan F, Damle PK, Litovchick L, Drapkin R, **Grossman SR**. CtBP determines ovarian cancer cell fate through repression of death receptors. Cell Death Dis 2020; 11:28

3. CtBP as a cancer therapeutic target

CtBP is a functional dehydrogenase enzyme, selectively active in cancer cells, and we were the first to characterize a small molecule inhibitor of CtBP (MTOB) that could selectively kill cancer cells and slow the growth of colon cancer xenografts. We found CtBP overexpressed in >50% of colon cancers suggesting CtBP could be a human oncogene, correlated with its many known oncogenic activities, such as survival, EMT, and migration/invasion. In collaboration with the Patel group, we demonstrated that CtBP chemical inhibition by MTOB or depletion by RNAi blocks colon cancer stem cell self-renewal and TCF4 transcriptional activation of C-myc. In collaboration with the Royer group, the structure of CtBP in complex with its substrate MTOB was solved, leading to the rational design of the 1st synthetic CtBP inhibitor, HIPP in collaboration with the Ellis group. The CtBP/HIPP structure was then solved with the Royer group, leading to further improvement of HIPP with the identification of chlorinated HIPP derivatives with nM IC50 values. We identified the mechanism of action of CtBP inhibitors as breaking CtBP oligomers via disruption of cycling of NADH/NAD+ through the active site. Ongoing and future work in this area will identify lead compounds for further pre-clinical and ultimately clinical testing in malignancies with CtBP overexpression, such as colon, breast, ovarian, and prostate cancer.

1. Hilbert BJ, Morris BL, Ellis KC, Paulsen JL, Schiffer CA, **Grossman SR***, Royer WE Jr*. Structure-Guided Design of a High Affinity Inhibitor to Human CtBP. ACS Chem Biol. 2015; 10:1118-1127. *co-corresponding authors
2. Korwar S, Morris BL, Parikh HI, Coover RA, Doughty TW, Love IM, Hilbert BJ, Royer WE Jr, Kellogg GE, **Grossman SR***, Ellis KC*. Design, synthesis, and biological evaluation of substrate-competitive inhibitors of C-terminal Binding Protein (CtBP). Bioorg Med Chem. 2016; 24:2707-2715. *co-corresponding authors
3. Dcona MM, Damle PK, Zarate-Perez F, Morris BL, Nawaz Z, Dennis MJ, Deng X, Korwar S, Singh S, Ellis KC, Royer WE, Bandyopadhyay D, Escalante C, **Grossman SR**. Active-site tryptophan, the target of anti-neoplastic CtBP inhibitors, mediates inhibitor disruption of CtBP oligomerization and transcription coregulatory activities. Mol Pharmacol 2019; 96:99-108.
4. Jecrois AM, Dcona MM, Deng X, Bandyopadhyay D, **Grossman SR**, Schiffer CA, Royer WE. CryoEM Structure of CtBP2 Confirms Tetrameric Architecture. Structure 2020, in press.

4. Regulation and oncogenic activity of mutant gain-of-function p53 protein in lung cancer

The mutant oncogenic or gain-of-function (GOF) p53 protein found in about half of human cancers accumulates to high levels in tumor cells, on the order of 100-1000-fold over wild-type p53 protein levels. This aberrant accumulation is key to many of the GOF activities of mutant p53, including cell cycle activation, survival under stress (including therapeutic stress), invasion/migration, and metastasis. The mechanism of GOF p53 stabilization is not completely understood, and our work in this area stemmed from a collaboration with researchers S. Deb and S.P. Deb, who are studying how GOF p53 mechanistically drives GOF phenotypes. We sought to understand the mechanism underlying aberrant GOF p53 stability in lung cancer cells, with the goal of therapeutics that could destabilize GOF p53, and restore levels below the oncogenic “GOF” threshold. Our work has shown that GOF p53 polyubiquitination is inhibited in lung cancer cells through a mechanism dependent on constitutively active signalling by the DNA damage checkpoint kinase ATM. ATM phosphorylation of p53 serine 15 results in blockade of polyubiquitination, and stabilization, and ATM inhibitors lead to restoration of GOF p53 polyubiquitination and destabilization of the protein. Moreover, examination of lung cancer cell populations reveals a distribution of GOF p53 abundances, with the highest abundances observed in cells with the most active DNA damage and ATM signalling-likely the result of replication stress, which our collaborative work shows is induced by GOF p53 driving excess replication origin firing via transactivation of the cyclin A and chk1 genes. The replication stress induced by GOF p53 is a vulnerability that has led to a therapeutic strategy of combining ATM and chk1 inhibitors to effectively kill lung cancer cells expressing GOF p53.

1. Frum RA, Love IM, Damle P, Mukhopadhyay ND, Palit Deb S, Deb S, **Grossman SR**. Constitutive Activation of DNA Damage Checkpoint Signaling Contributes to Mutant p53 Accumulation via Modulation of p53 Ubiquitination. Mol Cancer Res. 2016; 14:423-436.

2. Vaughan CA, Pearsall I, Singh S, Windle B, Deb SP, **Grossman SR**, Yeudall WA, Deb S. Addiction of lung cancer cells to GOF p53 is promoted by up-regulation of epidermal growth factor receptor through multiple contacts with p53 transactivation domain and promoter. Oncotarget 2016; 7:12426-12446.
3. Singh S, Vaughan C, Frum R, **Grossman SR**, Deb S, Deb SP. Mutant p53 establishes targetable tumor dependency by promoting unscheduled replication. J Clin Invest. 2017; 127:1839-1855
4. Ding B, Haidurov A, Chawla A, Parmigiani A, van de Kamp G, Dalina A, Yuan F, Lee JH, Chumakov PM, **Grossman SR**, Budanov AV. 53-inducible SESTRINs might play opposite roles in the regulation of early and late stages of lung carcinogenesis. Oncotarget 2019; 10:6997-7009.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1dU8bhU2dMU5e/bibliography/43521573/public/?sort=date&direction=ascending

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D. Research Support

Ongoing Research Support

OC170094 Grossman (PI) 05/01/18 to 04/30/21 (NCE) Department of Defense
Role of C-terminal Binding Protein as Oncogene and Therapeutic Target in Epithelial Ovarian Cancer
The goals of this grant are to: 1) Establish CtBP as a transforming oncogene and dependency in ovarian cancer and normal fallopian tube epithelial cells; 2) Characterize the role of CtBP overexpression in human ovarian carcinogenesis and validate pharmacologic inhibition of CtBP in HGSOC orthotopic xenografts; 3) Develop a fallopian tube-specific transgenic mouse model for CtBP-driven ovarian carcinogenesis.

1R01GM119014-01 Royer (PI) 04/01/2017 - 01/31/2021 NIGMS/NIH
Structure-based characterization of CtBP as a therapeutic target in cancer
The goal of this grant is to use structural and biophysical techniques to correlate the potency of CtBP inhibitors with their ability to disrupt CtBP2 cellular functions and illuminate the connection between CtBP2 enzymatic catalysis and its co-transcriptional function.
Role: Co-investigator

5130582ST Deb (PI) 07/01/19- 06/30/21 Commonwealth (VA) Health Research Board
Targeting mutant p53-dependent checkpoints of genome duplication in lung cancer
The goal of this grant is to develop novel targeted therapy for lung cancer expressing mutant p53
Role: Co-investigator

1R21CA216685-01A1 Oh (PI) 04/01/18 to 03/31/21 (NCE) NCI/NIH
Therapeutic potential of neutrophil protease inhibitors in colon cancer
Role: Co-investigator

Completed Research Support (within 3 years)

5P30 CA016059-36 Winn (PI) 05/01/2017 to 04/30/2022 NCI/NIH
Massey Cancer Center Core Support Grant
Role: Deputy Director

5R01CA172660-06 Grossman (PI) 02/01/2013-01/31/2019 NCI/NIH
The Role of p53-inducible Sesn1 and Sesn2 genes in lung carcinogenesis