BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Daniel Geoffrey Tenen	Director, Cancer Science Institute of Singapore Professor of Medicine, Harvard Medical School
eRA COMMONS USER NAME (credential, e.g., agency login) DANTENEN	

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
University of California, Los Angeles	BA	06/71	Applied Math/Physical Chemistry
Harvard Medical School, Boston, MA	MD	06/75	Medicine
Brigham and Women's Hospital	Residency	06/82	Internal Medicine
Dana Farber Cancer Institute	Clin Fellow	06/83	Medical Oncology
Dana Farber Cancer Institute	Res Fellow	06/83	Gene regulation

A. Personal Statement

My research interests focus on gene regulation in both normal differentiation and cancer. Over the past 33 years my laboratory has made seminal contributions to understanding the role of gene regulation in cell differentiation and the role of disruption of these pathways in leukemia, lung cancer, and liver cancer. These efforts have included basic studies understanding gene regulation in normal and leukemic hematopoietic stem cells, leading to development of novel ways of manipulating gene expression and exploiting differences between normal and leukemic stem cells as a basis for targeted therapy, and the role of stem cell oncofetal proteins in leukemia and solid tumors, especially in liver cancer. In addition to my role as PI on many individual NIH R01 grants, I have also served as PI on Program Project grants and as Director of the Blood Program of the Harvard Stem Cell Institute. Since 2008, I have been Director of the Cancer Science Institute, National University of Singapore. My recent studies have focused on noncoding RNAs, and include published findings on antisense RNAs, RNA editing, and noncoding RNAs in gene regulation, methylation, and cancer. Our recent studies demonstrated that RNA can regulate DNA methylation, and that RNA can be utilized to induce demethylation in a gene-specific manner. If successful, potential future clinical applications could include the ability to specifically reverse disease related DNA methylation, such as methylation and/or of tumor suppressor genes.

B. Positions and Honors:

1975-1982 Residency in Internal Medicine, Peter Bent Brigham Hospital, Boston, MA, and Research Fellow, Dana Farber Cancer Institute, Boston, MA
1982-1983 Fellow in Medical Oncology, Dana Farber Cancer Institute, Boston, MA:
1984-1986 Instructor in Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
1986-1994 Assistant Professor of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
1994-1999 Associate Professor of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
1999- Professor of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
2004- Program Director, Blood Program, Harvard Stem Cell Institute
2008- Director, Cancer Science Institute and Professor of Medicine, National University of Singapore

Honors and Advisory Committee Memberships:

1989-1994 Scholar, Leukemia Society of America
1997-2001 Hematology Study Section, National Institutes of Health
1998 Scientific Program Director, Annual Meeting of the American Society of Hematology
2015 Outstanding Investigator Award, National Cancer Institute

C. Contributions to Science

1) Transcription factors play the critical role in normal myeloid cell development.

When starting my own laboratory in 1984, it was accepted that differentiation of hematopoietic cells was largely the result of the actions of specific cytokines, such as the granulocyte stimulating factor (G-CSF). We took a different approach, working from the most mature myeloid genes backwards to the stem and progenitor cells. We first cloned myeloid specific cDNAs, then the promoters, and identified three common transcription factors, Runx1, PU.1, and C/EBPalpha (Runx1 became the focus on studies of my colleague Dong-Er Zhang). We developed a conditional knockout which demonstrated that PU.1 is indeed essential for HSC function and differentiation of the hematopoietic stem cell (HSC) into the earliest multipotential progenitors as well as mature granulocytes and macrophages (Iwasaki, 1995). For C/EBPalpha, we demonstrated through non-conditional and conditional knockout studies that it was absolutely essential for the development of granulocytic cells in steady state hematopoiesis, and that it played a role in HSC function as well (Zhang, 1997; Zhang, 2004; Ye, 2013). These and other studies confirmed the first part of our hypothesis, that lineage specific transcription factors, and not cytokines, were necessary and sufficient for stem cell function and differentiation. We also demonstrated the general applicability of these findings to other tissues, such as lung.

a. Iwasaki H, Somoza C, Shigematsu H, Duprez EA, Iwasaki-Arai J, Mizuno SI, Arinobu Y, Geary K, Zhang P, Dayaram T, Fenyus ML, Elf S, Chan S, Kastner P, Huettner CS, Murray R, Tenen DG, Akashi K. Distinctive and indispensable roles of PU.1 in maintenance of hematopoietic stem cells and their differentiation. 2005: Blood 106:1590-1600.
b. Zhang D E, Zhang P, Wang N, Hetherington CJ, Darlington GJ, Tenen DG. Absence of granulocyte colony-stimulating factor signaling and neutrophil development in CCAAT enhancer binding protein alpha deficient mice. 1997: PNAS 94:569-574.
c. Zhang P, Iwasaki-Arai J, Iwasaki H, Fenyus ML, Dayaram T, Owens BM, Shigematsu H, Levantini E, Huettner CS, Lekstrom-Himes JA, Akashi K, Tenen DG. Enhancement of hematopoietic stem cell repopulating capacity and self-renewal in the absence of the transcription factor CCAAT Enhancer Binding Protein alpha. 2004: Immunity 21:853-863.
d. Ye M, Zhang H, Amabile G, Yang H, Staber PB, Zhang P, Levantini E, Alberich-Jordà M, Zhang J, Kawasaki A, Tenen DG. C/EBPa controls acquisition and maintenance of adult hematopoietic stem cell quiescence. 2013. Nature Cell Biol. 15:385-94. PMCID: PMC3781213

2) Disruption of myeloid transcription factors are a critical event in the pathogenesis of Acute Myeloid Leukemia (AML).

Based on these findings, we hypothesized that in acute myeloid leukemia (AML), defined by a block in differentiation, the function of these lineage specific transcription factors would by necessity be disrupted by multiple mechanisms. We demonstrated disruption of C/EBPalpha and/or PU.1 by mutation (Pabst, 2001a), downregulation of expression (Pabst, 2001b), and function, the latter mediated by fusion protein products of common translocations (Mueller, 2006) and/or by post-translational modification mediated by activated mutant kinases (Radomska, 2006). These findings established the role of these factors in leukemogenesis, as well as in lung cancer. The importance of these findings is that detection of C/EBPa mutations are part of the classification and diagnostic workup for AML. Furthermore, they demonstrated that drugs targeting fusion proteins and mutant kinases work in part through restoring these factors.

a. Pabst T, Mueller BU, Zhang P, Radomska HS, Narravula S, Schnittger S, Behre G, Hiddemann W, Tenen DG. Dominant-negative mutations of *CEBPA*, encoding CCAAT/Enhancer Binding Protein-α (C/EBPα) in acute myeloid leukemia. 2001: Nature Genetics 27:263-270.
b. Radomska HS, Bassères DS, Zheng R, Zhang P, Dayaram T, Yamamoto Y, Sternberg DW, Lokker N, Giese NA, Bohlander S, Schnittger S, Delmotte MH, Davis RJ, Small D, Hiddemann W, Gilliland DG, Tenen DG. Block of C/EBPα Function by Phosphorylation in Acute Myeloid Leukemia with FLT3. 2006: J Exp Med 203:371-381.
c. Ye M, Zhang H, Yang H, Koche R, Staber PB, Cusan M, Levantini E, Welner RS, Bach CS, Zhang J, Krivtsov A, Armstrong SA, Tenen DG. Hematopoietic differentiation is required for initiation of acute myeloid leukemia. 2015. Cell Stem Cell 17:611-623.
d. Bararia B, Kwok HS, Welner RS, Numata A, Sa´rosi MB, Yang H, Wee S, Tschuri S, Ray D, Weigert O, Levantini E, Ebralidze AK, Gunaratne J, Tenen DG. Acetylation of C/EBPα inhibits its granulopoietic function. 2016. Nature Comm. 7:10968.

3) Lineage specific transcription factors act as tumor suppressors, and graded reduction leads to tumorigenesis.

Previous studies had established a role for “classic” tumor suppressors, such as p53 and RB, but our work established that these lineage specific factors also acted like tumor suppressors. We conducted a series of studies demonstrating that these lineage specific transcription factors can also act as tumor suppressors. The most dramatic example was a hypomorphic series of mouse models in which reduction of PU.1 levels from 50% wild type (heterozygote knockouts) to 20% resulted in development of AML (Rosenbauer, 2004; Rosenbauer, 2006, Steidl, 2006). We also demonstrated that these effects are likely due to hyperproliferation

of HSCs when lineage specific transcription factor levels are decreased (Staber, 2013). These findings have set an important precedent for subsequent findings by other investigators.

a. Rosenbauer F, Wagner K, Kutok JL, Iwasaki H, Le Beau MM, Okuno Y, Akashi K, Fiering S, Tenen DG. Acute myeloid leukemia induced by graded reduction of a lineage-specific transcription factor, PU.1. 2004: Nature Genet. 36:624-630.
b. Rosenbauer F, Owens BM, Yu L, Tumang JR, Steidl U, Kutok JL, Clayton LK, Wagner K, Scheller M, Iwasaki H, Liu C, Hackanson B, Akashi K, Leutz A, Rothstein TL, Plass C, Tenen DG. Lymphoid cell growth and transformation suppressed by a key regulatory element of the gene encoding PU.1. 2006: Nature Genet. 38:27-27.
c. Steidl U, Rosenbauer F, Verhaak RGW, Gu X, Ebralidze A, Otu HH, Klippel S, Steidl C, Bruns I, Costa DB, Wagner K, Aivado M, Kobbe G, Valk PJ, Passegué E, Libermann TA, Delwel R, Tenen DG. Essential role of Jun family transcription factors in PU.1-induced leukemic stem cells. 2006. Nature Genet 38:1269-1277.
d. Staber PB, Zhang P, Ye M, Welner R, Nombela-Arrieta C, Bach C; Kerenyi M, Bartholdy BA, Zhang H; Alberich-Jorda M, Lee S, Yang H, Ng F, Zhang J, Leddin M, Silberstein LE, Hoefler G, Gottgens B, Rosenbauer F, Huang G, Tenen DG. Sustained PU.1 Levels Balance Cell Cycle Regulators to Prevent Exhaustion of Adult Hematopoietic Stem Cells. 2013. Molecular Cell 49:934-46. PMCID: PMC3644723,

4) An alternative role for hematopoietic transcription factors in solid tumors.

While our studies have focused on the hematopoietic system and leukemia, they have general applicability to other cancers as well. The same studies that hypothesized that transcription factors played a specific role in blood differentiation could be applied to the lung, in which knockout of C/EBPa led to a specific block in alveolar cell differentiation (Basseres, 2006). In addition, we could demonstrate that C/EBPa is an important tumor suppressor in human lung cancer (Halmos, 2002), a finding confirmed by multiple other groups. In addition, we have worked on a number of studies in lung cancer, including the first report of mechanism of resistance to EGFR receptor in lung cancer (Kobayashi, 2005). Finally, we have recently demonstrated the role of an embryonic transcription factor (SALL4), expressed in adult HSC, is ectopically re-activated in many adult solid tumors, and that it can serve as a useful prognostic marker as well as therapeutic target (Yong, 2013).

a. Halmos B, Huettner CS, Kocher O, Ferenczi K, Karp DD, Tenen DG. Downregulation and antiproliferative role of C/EBPα in lung cancer. 2002: Cancer Res 62:528-534.
b. Kobayashi S, Boggon TJ, Dayaram T, Jänne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG*, Halmos B*. Emergence of a drug-resistance mutation in the epidermal growth factor receptor gene in gefitinib-responsive non-small cell lung cancer. 2005: New England Journal of Medicine 352:786-792. *Co-corresponding authors.
c. Yong KJ, Gao C, Lim JSJ, Yan B, Yang H, Dimitrov T, Kawasaki A, Ong CW, Wong KF, Lee S, Ravikumar S, Srivastava S, Tian X, Poon RT, Fan ST, Luk JM, Dan YY, Salto-Tellez M, Chai L, Tenen DG. Oncofetal Gene SALL4 Defines an Aggressive Hepatocellular Carcinoma Subtype. 2013. N Engl J Med 368:2266-76. PMCID: PMC3781214
d. Yong KJ, Basseres DS, Welner RS, Wen Cai Zhang WC, Yang H, Yan B, Alberich-Jorda M, Zhang J, de Figueiredo-Pontes LL, Battelli C, Hetherington CJ, Ye M, Zhang H, Maroni G, O'Brien K, Magli MC, Borczuk AC, Varticovski L, Kocher O, Zhang P, Moon YC, Sydorenko N, Cao L, Davis TW, Thakkar BM1, Soo RA, Iwama A, Lim B, Halmos B, Neuberg D, **Tenen DG***, Levantini E*. Targeted BMI1 inhibition impairs tumor growth in lung adenocarcinomas showing low CEBPα expression. 2016. Sci Transl Med 8:350ra104. *Co-last authorship.

5) noncoding RNAs (ncRNAs) and RNA editing play multifaceted roles in cancer.

In recent years, my laboratory has focused on the role of RNA in regulation of normal hematopoietic cells and cancer. We initiated these studies with identification of a long noncoding antisense RNA in the PU.1 locus (Ebralidze, 2008). These studies demonstrated several important principles: (1) these noncoding RNAs can serve to restrict expression of master regulatory genes such as PU.1 in lineages in which PU.1 must be suppressed, such as T cells; (2) they can be discrete RNAs with discrete promoters, and use distal regulatory elements which are shared with the mRNA, with a specific chromatin configuration; and (3), importantly for this proposal, knockdown of these antisense RNAs can result in upregulation of the tumor suppressor PU.1 in leukemic cells in which it is suppressed, a potential therapeutic approach. In addition, I have become very interested in the role of dysregulation of RNA editing in cancer, and was a senior author of a seminal paper describing for the first time how a specific RNA editing event could activate genes in the myc pathway to contribute to liver cancer development (Chen, 2013). This is a paradigm shift, in that it demonstrates how non-DNA mutational mechanisms can lead to genetic changes in cancer. We will continue these studies in AML in this proposal. Finally, we have undertaken groundbreaking studies, demonstrated that RNA regulates DNA methylation, and that RNA can be utilized to induce demethylation in a gene-specific manner (Di Ruscio, 2013). These studies could potentially lead to novel therapeutic modalities, especially in diseases which seem to respond to inhibition of DNA methylation. Importantly, while many investigators have initiated studies on the

role of RNA, these three types of studies are very novel and currently being investigated by relatively few groups.

a. Ebralidze AK, Guibal FC, Steidl U, Zhang P, Lee S, Bartholdy B, Alberich Jorda M, Petkova V, Rosenbauer F, Huang G, Dayaram T, Klupp J, O'Brien K, Will B, Hoogenkamp M, Borden K, Bonifer C, Tenen DG. PU.1 expression is modulated by the balance of functional sense and antisense RNAs regulated by a shared cis-regulatory element. 2008. Genes Dev 22:2085-2092. PMCID: PMC2492744.
b. Chen L, Li Y, Lin CH, Chan TH, Chow RK, Song Y, Liu M, Yuan YF, Fu L, Kong KL, Qi L, Li Y, Zhang N, Tong AH, Kwong DL, Man K, Lo CM, Lok S, Tenen DG*, Guan XY*. Recoding RNA editing of AZIN1 predisposes to hepatocellular carcinoma. 2013. Nat Med. 19:209-16. PubMed Central PMCID: PMC3783260. *Co-corresponding authors.
c. Chan TH, Lin CH, Qi L, Fei J, Li Y, Yong KJ, Liu M, Song Y, Chow RK, Ng VH, Yuan YF, Tenen DG, Guan XY, Chen L. A disrupted RNA editing balance mediated by ADARs (Adenosine DeAminases that act on RNA) in human hepatocellular carcinoma. 2014. Gut 63:832-843. PMCID: PMC journal in process.
d. Di Ruscio A, Ebralidze AK, Benoukraf T, Amabile G, Goff LA, Terragni J, Figueroa ME, De Figureido Pontes LL, Alberich-Jorda M, Zhang P, Wu M, D'Alò F, Melnick A, Leone G, Ebralidze KK, Pradhan S, Rinn JL, Tenen DG. DNMT1-interacting RNAs block gene specific DNA methylation. 2013. Nature 503:371-376. PubMed Central PMCID: PMC3870304.

Complete List of Published Work in PubMed:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Tenen+DG