BIOGRAPHICAL SKETCH

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NAME: Daniel Geoffrey Tenen

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POSITION TITLE: Professor of Medicine, Harvard Medical School

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
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	06/84	Gene regulation

A. Personal Statement

I was born and raised in Southern California, attended UCLA with a major in Applied Math and Physical Chemistry and Harvard Medical School, with postdoctoral research training in the laboratory of David Livingston at Dana Farber Cancer Institute, as well as clinical training with a residency in internal medicine at Brigham and Women's Hospital and Board Certification in Medical Oncology at Dana Farber. I established my own independent laboratory in 1984 at Beth Israel Deaconess Medical Center, Harvard Medical School, and also since 2008 at the Cancer Science Institute Singapore, where I served as founding Director until 2020.

For the past 38 years my lab has studied gene regulation in normal differentiation and cancer, initially with a focus on myeloid development and acute myeloid leukemia (AML). My laboratory has contributed to understanding the role of transcription factors in cell differentiation and disruption of these pathways in leukemia, lung cancer, and liver cancer. Current efforts include basic studies understanding gene regulation with an aim to manipulate gene expression in in normal and cancer stem cells as well as exploiting differences as a basis for targeted stem cell therapy. In addition to my research accomplishments, I have mentored many graduate students and postdoctoral fellows, many of whom are now full professors. I have served on many review boards, including NIH Study Sections and the Special Emphasis Panel which reviews candidates for the NCI Outstanding Investigator Award.

In addition to my studies on the role of transcription factors (DNA binding proteins) in normal hematopoiesis and leukemia, in the last decade I have in addition studied the role of nuclear long noncoding RNAs in mRNA transcription, epigenetic memory, DNA methylation, DNA replication, and cancer.

In addition, since 2005 I have collaborated with Li Chai on the role of the stem cell oncofetal protein SALL4 in leukemia and solid tumors, especially liver cancer.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2008-2020 Director, Cancer Science Institute of Singapore
2004- Program Leader, Blood Program, Harvard Stem Cell Institute
1999- Professor of Medicine, Harvard Medical School, Boston, MA
1994-1999 Associate Professor of Medicine, Harvard Medical School, Boston, MA

1986-1994 Assistant Professor of Medicine, Harvard Medical School, Boston, MA
1984-1986 Instructor in Medicine, Harvard Medical School, Boston, MA
1982-1983 Fellow in Medical Oncology, Dana Farber Cancer Institute, Boston, MA (Board certified in Medical Oncology in Massachusetts)
1975-1982 Residency in Internal Medicine, Peter Bent Brigham Hospital, Boston, MA, and Research Fellow, Dana Farber Cancer Institute, Boston, MA (Board certified in Internal Medicine in Massachusetts)

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 CEBPA (Runx1 was the focus of 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 CEBPA, 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; 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. More recent studies have demonstrated the role of the transcription factor ZNF143 in mediating CTCF dependent promoter-enhancer loops, which are critical for proper gene expression and hematopoietic stem cell function (Zhou, 2021).

a. Zhang D E, …., **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.
b. Iwasaki H … , **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. *co-last/corresponding author.
c. Ye M, …**Tenen DG**. C/EBPa controls acquisition and maintenance of adult hematopoietic stem cell quiescence. 2013. Nature Cell Biol. 15:385-94.
d. Zhou, Q, … **Tenen DG**. ZNF143 mediates CTCF-bound promoter-enhancer loops required for murine hematopoietic stem and progenitor cell function. 2021. Nature Communications 12:43.

2) Lineage specific transcription factors act as tumor suppressors, and graded reduction leads to tumorigenesis in Acute Myeloid Leukemia (AML)

We hypothesized that in 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 CEBPA and/or PU.1 by mutation (Pabst, 2001), downregulation of expression, and function, the latter mediated by fusion protein products of common translocations and/or by post-translational modification mediated by activated mutant kinases. 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 CEBPA 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. In addition, 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. 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). We also demonstrated stem cell have to progress to a progenitor stage to initiate AML (Ye, 2015). These findings have set an important precedent for subsequent findings by other investigators.

a. Pabst T… **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. Rosenbauer F ….**Tenen DG.** Acute myeloid leukemia induced by graded reduction of a lineage-specific transcription factor, PU.1. 2004: Nature Genet. 36:624-630.
c. Zhang H ….**Tenen DG**. Sox4 is a key oncogenic target in C/EBPα mutant Acute Myeloid Leukemia. 2013. Cancer Cell 24: 575–588.
d. 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.

3) The role of lineage specific transcription factors and epigenetic modulators in lung cancer

Our studies on the hematopoietic system and leukemia have general applicability to other cancers as well. The same studies that hypothesized that transcription factors played a specific role in blood differentiation were applied to the lung, demonstrating that knockout of CEBPA led to a specific block in alveolar cell differentiation (Basseres, 2006). In addition, we demonstrated that CEBPA is an important tumor suppressor in human lung cancer (Halmos, 2002), a finding confirmed by multiple other groups. Furthermore, we have gone on to demonstrate that CEBPA low lung adenocarcinomas express high levels of the polycomb protein BMI1, and have demonstrated proof of principle that these cancers would respond to a BMI1 inhibitor which is currently in clinical trials. In addition, we have worked on a number of other studies in lung cancer, including the first report of mechanism of resistance to EGFR receptor in lung cancer (Kobayashi, 2005). More recently, we have demonstrated the role of BMI1 and the fatty acid pathway in EGFR mutated lung cancer, as well as identifying a novel targetable epithelial population in KRAS mutant non-small cell lung cancer, representing studies suggesting novel therapeutic approaches.

a. Halmos B … **Tenen DG**. Downregulation and antiproliferative role of C/EBPα in lung cancer. 2002: Cancer Res 62:528-534.
b. Kobayashi S … **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 last/corresponding author.
c. Yong KJ … **Tenen DG***, Levantini E. Targeted BMI1 inhibition impairs tumor growth in lung adenocarcinomas showing low CEBPA expression. 2016. Sci Transl Med 8:350ra104. *Co-last authorship.
d. Maroni G … **Tenen DG***, Levantini E. Identification of a targetable KRAS-mutant epithelial population in Non-Small Cell Lung Cancer. 2021. Commun Biol. 4:370. *co last/corresponding author.

4) Reactivation of the oncofetal protein SALL4 to drive self-renewal in multiple adult human cancers, including AML, lung, and hepatocellular cancer.

We demonstrated that SALL4, an important embryonic transcription factor, 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). Work performed with our collaborator Li Chai demonstrated the role of SALL4 in myelodysplastic syndrome (MDS) and leukemias (Gao, 2013; PMID 23287862). As SALL4 is normally not expressed in most adult tissues, one therapeutic approach is to knock it down or induce its degradation. A second approach is to disrupt the SALL4-NuRD co-repressor complex (Yong, 2013), and to enhance development of small molecules we determined the structure of the SALL4 amino terminus with NuRD (Liu, 2018). A third therapeutic approach to SALL4+ tumors would be to target downstream metabolic pathways, and indeed we have demonstrated that SALL4 induces oxidative metabolism which respond to oxidative phosphorylation inhibition (Tan, 2019; PMID 31446059). Thus we have uncovered 3 approaches to targeting SALL4, which drives self-renewal in a large percentage (25-30%) in tumors of lung, liver, brain, breast, endometrium, ovary, and others, with a goal to develop therapeutics for clinical efficacy in humans. We have also recently characterized a novel mechanism of how RNA can induce demethylation to activate SALL4 (Kwon, 2021; PMID 34597139), and that this can be used to induce vulnerability in cancer (Yang, 2021). Finally, we have demonstrated that hypomethylation therapy, used to treat a number of cancers, can induce an oncogene (SALL4) and poor overall survival (Liu YC, 2022, accepted).

a. Yong KJ … Chai L, **Tenen DG**. Oncofetal Gene SALL4 Defines an Aggressive Hepatocellular Carcinoma Subtype. 2013. N Engl J Med 368:2266-76.

b. Liu BH … Chai L, Sivaraman J, **Tenen DG**. Targeting cancer addiction for SALL4 by shifting its transcriptome with a pharmacologic peptide. 2018. PNAS 115:E7119-E7128.
c. Yang J ... **Tenen DG***, Chai L. Targeting an Inducible SALL4-Mediated Cancer Vulnerability with Sequential Therapy. 2021. Cancer Res. 81:6018-6028. *co last/co-communicating author.
d. Liu YC, Kwon J, ... Bassal MA, Voso MT, **Tenen DG***, Chai, L. Demethylation and Up-Regulation of an Oncogene after Hypomethylating Therapy. 2022. N Engl J Med. 386:1998-2010. PMID: 35613022. *co last/co-communicating author

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), 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. This is a paradigm shift, in that it demonstrates how non-DNA mutational mechanisms can lead to genetic changes in cancer. 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. Recent studies have demonstrated the role of enhancer RNAs which direct gene expression by promoting enhancer-promoter interactions which are disrupted in leukemia (Trinh, 2021), as well as the role of a SALL4 pseudogene RNA in demethylating and activating the oncogene SALL4 in liver cancer cells (Kwon, 2021).

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.
b. Di Ruscio A, Ebralidze AK…**Tenen DG**. DNMT1-interacting RNAs block gene specific DNA methylation. 2013. Nature 503:371-376.
c. Trinh BQ, ... **Tenen DG.** Myeloid lncRNA LOUP Mediates Opposing Regulatory Effects of RUNX1 and RUNX1-ETO in t(8;21) AML. 2021. Blood 138:1331-1344. PMID: 33971010.
d. Kwon J, ... Di Ruscio A, Tay Y, Chai L, **Tenen DG**. Pseudogene-mediated DNA demethylation leads to oncogene activation. 2021. Science Advances eabg1695. PMID 34597139.

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