BIOGRAPHICAL SKETCH

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NAME: Benjamin Tycko

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

POSITION TITLE: Professor of Pathology

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	B.A.	1979	Biochemistry
New York University School of Medicine	M.D.	1984	Medicine
New York University School of Medicine	Ph.D.	1984	Medical Sciences

A. Personal Statement

My lab has a long-standing research program on genetics and epigenetics in human development and disease. Our recent work has involved genome-wide and locus-specific profiling of CpG methylation, both net and allele-specific, for disease gene discovery and pathway analysis in Down syndrome, autoimmune diseases, neuropsychiatric disorders, and cancers.

1. Kerkel K, Spadola A, Yuan E, Kosek J, Jiang L, Hod E, Li K, Murty VV, Schupf N, Vilain E, Morris M, Haghighi F, Tycko B (2008) Genomic surveys by methylation-sensitive SNP analysis identify sequence-dependent allele-specific DNA methylation. Nat Genet 40:904-908. PMID: 18568024
2. Shakya R, Gonda T, Quante M, Salas M, Kim S, Brooks J, Hirsch S, Davies J, Cullo A, Olive K, Wang TC, Szabolcs M, Tycko B[#], Ludwig T (2013) Hypomethylating therapy in an aggressive stroma-rich model of pancreatic carcinoma. Cancer Res 73:885-96. PMID: 23204224, PMCID: PMC3548986 ([#]corresponding author)
3. Mendioroz M, Do C, Jiang X, Liu C, Darbary H, Lang CF, Lin J, Thomas A, Abu-Amero S, Stanier P, Temkin A, Yale A, Liu M-M, Li Y, Salas M, Kerkel K, Capone G, Silverman W, Yu Y.E., Moore G, Wegiel J, Tycko B (2015). Trans-effects of chromosome aneuploidies on DNA methylation patterns in human Down syndrome and mouse models. Genome Biology 16:263. PMID: 26607552, PubMed Central PMCID: PMC4659173
4. Do C, Lang CF, Lin J, Darbary H, Krupska I, Velander C, Nagy PL, Petukhova L, Vonsattel JP, Clynes RA, Dwork, AJ, Kral, JG, Monk, C, Christiano, AM, Tycko, B (2016) Mechanisms and disease associations of haplotype-dependent allele specific DNA methylation. Am J of Hum Genet 98: 934-955. PubMed PMID: 27153397; PubMed Central PMCID: PMC4863666

B. Positions and Honors

Professional Experience:

1984-1986	Stanford University Hospital	Resident in Pathology
1986-1989	Stanford University	Post-doctoral Fellow
1989-1991	Harvard University	Instructor in Pathology
1991-1996	Columbia University	Assistant Professor of Pathology
1996-2007	Columbia University	Associate Professor of Pathology
2007-2017	Columbia University	Professor of Pathology

2017-current Hackensack University Medical Center Senior Scientist, Dept. Biomedical Research

Other Experience and Professional Memberships:

Member, Pathology B and CG Study Sections, N.I.H. (2000-2004)
Ad hoc reviewer, Genetics in Health and Disease Study Sections (several meetings 2005- 2016)
Ad hoc reviewer, Cancer Center Support Grants (several site visits 2010 – 2017)

Associate Director for Shared Resources, Herbert Irving Comprehensive Cancer Center (2008-2017)

Honors:

Medical	Alpha Omega Alpha Society
Post-doctoral	National Research Service Award (NIH)
Post-Graduate	Harold Golden Lamport Research Award, Columbia University
	Solomon A. Berson Medical Alumni Achievement Award, New York University

C. Contributions to Science (from a total of 159 peer-reviewed publications)

My graduate studies at NYU in the lab of Dr. Fred Maxfield, dealt with the cell biology of endocytosis and my post-doctoral work at Stanford in the lab of Jeffrey Sklar dealt with chromosomal translocations in normal and leukemic T lymphocytes. My 1982 *Cell* paper with Maxfield was the first to report rapid acidification of endosomes, with important implications for receptor recycling and viral entry to cells. My 1989 *Science* paper with Sklar was the first to report chimeric T cell receptors due to chromosomal trans-rearrangements in normal human lymphocytes, with implications for antigen receptor diversity and leukemogenesis.

1. My initial discoveries and publications as an independent investigator dealt with genomic imprinting in normal human tissues and the role of imprinted and non-imprinted genes in Wilms tumors. Our 1992 paper, in the inaugural issue of *Nature Genetics*, was the first report of a gene with monoallelic expression due to genomic imprinting in humans. Our subsequent studies using genomic and epigenomic approaches implicated altered imprinting in Wilms tumors, where sequences in and upstream of the H19 gene frequently show gains of CpG methylation, causing H19 gene silencing and activating the linked and oppositely imprinted IGF2 gene. In a different sub-group of Wilms tumors, those with beta-catenin mutations, we elucidated the important downstream Wnt/beta-catenin target genes, and provided genetic data establishing a nearly invariant link between WT1 mutations and stabilizing mutations in the beta-catenin (CTNNB1) gene, which together define a class of these tumors that is mutually exclusive with those that have epigenetic lesions in H19/IGF2.

a. Zhang Y and Tycko B (1992). Monoallelic expression of the human H19 gene. Nat Genet 1:40-44. PMID: 1363808
b. Moulton T, Crenshaw T, Hao Y, Moosikasuwan J, Lin N, Dembitzer F, Hensle T, Weiss L, McMorrow L, Loew T, Gerald W and Tycko B (1994). Epigenetic lesions at the H19 locus in Wilms' tumour patients. Nat Genet 7:440-447. PMID: 8391213
c. O'Keefe D, Dao D, Zhao L, Sanderson R, Warburton D, Weiss L, Anyane-Yeboa K and Tycko B (1997). Coding mutations in p57KIP2 are present in some cases of Beckwith-Wiedemann syndrome but are rare or absent in Wilms tumors. Am J Hum Genet 61:295-303. PMID: 9311733
d. Li C-M, Kim CE, Margolin AA, Guo M, Zhu J, Mason JM, Hensle TW, Murty VVS, Grundy PE, Fearon ER, D'Agati V, Licht JD, Tycko B (2004) CTNNB1 mutations and over-expression of Wnt/beta-catenin target genes in WT1-mutant Wilms tumors. Am J Pathol, 156: 1943-1953. PMID: 15579438, PMCID: PMC16187272.

2. My lab also has a long-standing research program on imprinted gene discovery, and the role of imprinted genes in placental and fetal growth. As reported in our papers between 1997 and 2013 we discovered and characterized several novel examples of imprinted genes. Gene discovery was initially by chromosome walking around known imprinted loci, and subsequently by an array-based genome-wide approach, called MSNP, that we developed. One of these imprinted genes, which we initially named *IPL* (Imprinted in Placenta and Liver), and then renamed *PHLDA2*, encodes a pleckstrin-homology domain protein that binds phosphoinositide lipids. We made KO mice for this gene and showed that it plays an important role in regulating growth of the placenta. Satisfyingly, subsequent work by others has identified genetic polymorphisms in the *PHLDA2* promoter region that influence human birthweight.

a. Qian N, Frank D, O'Keefe D, Dao D, Zhao L, Yuan L, Wang Q, Keating M, Walsh C and Tycko B (1997). The IPL gene on chromosome 11p15.5 is imprinted in humans and mice and is similar to TDAG51, implicated in Fas expression and apoptosis. Hum Mol Genet 6:2021-2029. PMID: 9328465
b. Frank D, Fortino W, Clark L, Musalo R, Wang W, Saxena A, Li C M, Reik W, Ludwig T and Tycko B (2002). Placental overgrowth in mice lacking the imprinted gene Ipl. Proc Natl Acad Sci U S A 99:7490-7495. PMID: 12032310
c. Salas M, John R, Saxena A, Barton S, Frank D, Fitzpatrick G, Higgins M J and Tycko B (2004). Placental growth retardation due to loss of imprinting of Phlda2. Mech Dev 121:1199-1210. PMID: 15327781
d. McMinn J, Wei M, Schupf N, Cusmai J, Johnson E B, Smith A C, Weksberg R, Thaker H M and Tycko B (2006). Unbalanced placental expression of imprinted genes in human intrauterine growth restriction. Placenta 27:540-549. PMID: 16125225

3. We carried out some of the earliest microarray-based studies of gene expression in Down syndrome, with findings on non-linear over-expression of specific genes that remain relevant today, and we made useful BAC-transgenic mouse models with physiologically realistic and faithful tissue-specific over-expression of important chromosome 21-linked genes. In our 2010 *PLoS Genetics* paper we reported our discovery of recurrent, gene-specific, alterations in DNA methylation in Down syndrome cells and tissues – a report that has opened a new field of research on trans-acting genetic-epigenetic interactions, with several papers now from other labs, and with a recently accepted comprehensive study of methylation patterns in DS vs. control brain cells and T cells from our lab. We also have a collaboration with others at Columbia and elsewhere in which we have been defining genetic modifiers of susceptibility to Alzheimer's disease in adults with DS.

a. Li C M, Guo M, Salas M, Schupf N, Silverman W, Zigman W B, Husain S, Warburton D, Thaker H and Tycko B (2006). Cell type-specific over-expression of chromosome 21 genes in fibroblasts and fetal hearts with trisomy 21. BMC Med Genet 7:24. PMID: 16539728
b. Altered DNA Methylation in Leukocytes with Trisomy 21. Kerkel K, Schupf N, Hatta K, Pang D, Salas M, Kratz A, Minden M, Murty VVS, Zigman WB, Mayeux RP, Jenkins EC, Torkamani A, Schork NJ, Silverman W, Croy BA, Tycko B (2010). Altered DNA Methylation in Leukocytes with Trisomy 21. PLoS Genet 6:e1001212. PMID: 21124956, PMCID: PMC2987931
c. Xing L, Salas M, Zhang H, Gittler J, Ludwig T, Lin CS, Murty VV, Silverman W, Arancio O, Tycko B (2013). Creation and characterization of BAC-transgenic mice with physiological overexpression of epitope-tagged RCAN1 (DSCR1). Mamm Genome 24:30-43. PMID: 23096997, PMCID: PMC3562396
d. Mendioroz M, Do C, Jiang X, Liu C, Darbary H, Lang CF, Lin J, Thomas A, Abu-Amero S, Stanier P, Temkin A, Yale A, Liu M-M, Li Y, Salas M, Kerkel K, Capone G, Silverman W, Yu Y.E., Moore G, Wegiel J, Tycko B (2015). Trans-effects of chromosome aneuploidies on DNA methylation patterns in human Down syndrome and mouse models. Genome Biology, 16:263. PMID: 26607552, PubMed Central PMCID: PMC4659173

4. We were among the first groups to study the role of epigenetics in stromal cells of human gastrointestinal cancers, and we are now studying the efficacy of DNA hypomethylating therapy, both in single-agent and combination therapy protocols, in a preclinical model of pancreatic cancer. In this same general line of work, we started a promising project on chemoprevention of gastric cancer in a mouse model using a methyl donor-rich diet, which is now being pushed forward by my longtime colleague and K-award mentee Tamas Gonda.

a. Jiang L, Gonda T, Gamble M, Salas M, Seshan V, Tu S, Twadell WS, Hegyi P, Lazar G, Steele I, Varro A, Wang TC, Tycko B (2008). Global hypomethylation of genomic DNA in cancer-associated myofibroblasts. *Cancer Res* 68:9900-9908. PMID: 19047171 PMCID: PMC267054
b. Quante M, Tu SP, Tomita H, Gonda T, Wang SS, Takashi S, Baik GH, Shibata W, Diprete B, Betz KS, Friedman R, Varro A, Tycko B, Wang TC. (2011) Bone marrow-derived myofibroblasts contribute to the mesenchymal stem cell niche and promote tumor growth. Cancer Cell 19(2):257-72. PMID: 21316604, PMCID: PMC3060401
c. Gonda TA, Kim Y-I, Salas M, Gamble MV, Shibata W, Muthupalani S, Sohn K-J, Abram J, Fox JG, Wang TC, Tycko B (2012). Folic acid increases global DNA methylation and reduces inflammation to prevent Helicobacter-associated gastric cancer in mice. *Gastroenterology.* 142(4):824-833 PMID: 22474448

d. Shakya R, Gonda T, Quante M, Salas M, Kim S, Brooks J, Hirsch S, Davies J, Cullo A, Olive K, Wang TC, Szabolcs M, Tycko B[#], Ludwig T (2013) Hypomethylating therapy in an aggressive stroma-rich model of pancreatic carcinoma. *Cancer Res* 73:885-96. PMID: 23204224, PMCID: PMC3548986 ([#]corresponding author)

5. My lab has a major research emphasis on the mechanisms and consequences of haplotype-dependent allele-specific DNA methylation. This phenomenon, a fundamental cis-interaction between the genome and epigenome, was glimpsed in early studies of VNTR loci in the mid-1980's but was first uncovered by my lab as a widespread feature of the human epigenome, as reported in our 2008 *Nature Genetics* paper. In fact, hap-ASM affects more loci than imprinting. In 2010 we proposed that mapping hap-ASM could be a useful practical tool for promoting genome-wide association study (GWAS) peaks to biological true-positives and homing in on bona fide regulatory sequence variants, an idea that has also been taken up by other groups. We are now using array-based methods and Methyl-Seq to generate high-resolution maps in primary tissues and overlapping these maps with GWAS data to pinpoint disease-associated regulatory sequence variants. Our 2013 paper in *PLoS Genetics* raised the possibility of a special involvement of polymorphic CTCF binding sites at insulator elements as underlying some examples of hap-ASM. In our more recent studies (Do, C et al., AJHG 2016; Do et al., Genome Biology 2017) we validate this mechanism, extend it to polymorphic transcription factor binding sites (TFBS), and test it using cross-species comparisons of TFBS sequences and their CpG methylation patterns.

a. Kerkel K, Spadola A, Yuan E, Kosek J, Jiang L, Hod E, Li K, Murty V, Schupf N, Vilain E, Morris M, Haghighi F, Tycko B (2008). Genomic surveys by methylation-sensitive SNP analysis identify sequence-dependent allele-specific DNA methylation. *Nature Genet* 40:904-908. PMID: 18568024
b. Paliwal A, Temkin AM, Kerkel K, Yale A, Yotova I, Drost N, Lax S, Nhan-Chang CL, Powell C, Borczuk A, Aviv A, Wapner R, Chen X, Nagy PL, Schork N, Do C, Torkamani A, Tycko B (2013) Comparative anatomy of chromosomal domains with imprinted and non-imprinted allele-specific DNA methylation. *PLoS Genet* 9(8):e1003622. PMID: 24009515, PMCID: PMC3757050.
c. Do C, Lang CF, Lin J, Darbary H, Krupska I, Velander C, Nagy PL, Petukhova L, Vonsattel JP, Clynes RA, Dwork, AJ, Kral, JG, Monk, C, Christiano, AM, Tycko, B (2016) Mechanisms and disease associations of haplotype-dependent allele specific DNA methylation. Am J of Hum Genet 98: 934-955.
d. Do C, Shearer A, Suzuki M, Gelernter J, Terry MB, Greally J, Tycko B (2017) Genetic-epigenetic interactions in cis: a major focus in the post-GWAS era. Genome Biology, 18:120.

Link to a full list of published work by Dr. Tycko through the publicly available digital database NCBI/PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=Tycko%20B. For completeness, Moulton T, Crenshaw T, et al. Nature Genetics 1994 is not retrieved by this search because of author list truncation by PubMed, but is retrieved at https://www.ncbi.nlm.nih.gov/pubmed/7920666

D. Research Support

Ongoing Research Support

1R01HD090180-01 **(MPI: Tycko and Yu)** 9/1/2017 – 8/31/2022
NIH
Epigenetics of Down syndrome
We will use Nextgen methylation sequencing applied to cell types from chromosomally engineered mouse models of DS, to investigate the molecular mechanisms by which a chromosomal aneuploidy leads to altered DNA methylation patterns across the genome.
Role: MPI

1 R21 AI133140-01 **(Tycko: PI)** 8/1/2017 – 7/31/2022
NIH
DNA elements underlying celiac and Crohn's disease susceptibility
We will carry out Methyl-Seq of human CD4+ and CD8+ T cells, and human peripheral blood monocytes, to map hap-ASM genome-wide. Since hap-ASM often reflects allele-specific transcription factor binding site (TFBS) or insulator occupancies, we will cross-validate our findings using an independent method, Assay for Transposase-Accessible Chromatin Sequencing (ATAC-Seq).

NIH R01AG051412 **(MPI: Schupf, Lott & Silverman, Tycko Co-I)** 10/01/2015-09/30/2020
Biomarkers of Down Syndrome
This multi-center project collects biosamples form individuals with Down syndrome, and investigates the utility of blood biomarkers and brain imaging for understanding progression to Alzheimer's disease in these individuals. Dr. Tycko's lab prepares DNA/RNA, serum, and plasma from blood samples.
Role: Co-Investigator

MRA 402803 **(Schwartz: PI, Tycko Co-I)** 05/15/2016 – 05/14/2019
Melanoma Research Alliance
Inhibition of BET Bromodomain Proteins in Uveal Melanoma
We will investigate the effects of BRD4 inhibition. We will utilize cell line, xenograft, and patient explant tumor models and will conduct a clinical trial to analyze the anti-tumor effects of BRD4 inhibition, analyze the genetic and epigenetic profiles in UM with BRD4 inhibition, and assess mechanisms of primary and secondary resistance to treatment.

U01NS100600 **(MPI: Honig & Marder, Tycko Co-I)** 10/01/2016 – 09/30/2021
NIH
Targeting Lewy Body Specific Pathology Using Biomarkers
This project is designed to discover biomarkers specific for Dementia with Lewy Bodies (DLB). We will recruit a cohort with DLB for longitudinal study. We will use our extensive brain bank resources to analyze Lewy body specific gene expression to develop biomarkers for early diagnosis and identification of therapeutic targets.
Role: Co-Investigator