BIOGRAPHICAL SKETCH

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NAME: Markowitz, Sanford D.

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

POSITION TITLE: Professor

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
Harvard College	AB (Summa Cum Laude)	07/1974	Chemistry/Physics
Yale University	MD, PhD	09/1980, 06/1980	Medicine/Cell Biology
University of Chicago	Residency	06/1984	Internal Medicine
National Cancer Institute	Fellowship	06/1987	Medical Oncology

A. Personal Statement

Dr. Sanford Markowitz is a medical oncologist who is nationally recognized for making multiple landmark discoveries in the genetics of gastrointestinal cancers. His seminal contributions include: **i)** discovering mutations in TGF-beta receptors (TGFBR2) in human cancers; **ii)** showing that specific targeting of a TGFBR2 mutational hotspot is the second hit that explains how and why colon cancer develops in Lynch syndrome; **iii)** discovering 15-PGDH as a TGF-beta effector and colon cancer suppressor; **iv)** discovering 15-PGDH as also a key negative regulator of tissue stem cell response after organ injury; **v)** co-developing the first in vivo active small molecule inhibitors of 15-PGDH, and **vi)** demonstrating these compounds speed tissue regeneration in multiple disease models, including healing colitis and lung fibrosis, blocking neurodegeneration in Alzheimer's and traumatic brain injury, and accelerating hematopoietic recovery after bone marrow transplant; **vii)** co-discovering aberrant DNA methylation of hMLH1 as the cause of non-familial (Lynch phenocopy) DNA repair deficient colon cancers; **viii)** discovering the role of aberrant DNA methylation of CDH1 in the genesis of Hereditary Diffuse Gastric Cancers; **ix)** discovering vimentin gene methylation as a sensitive and specific biomarker of colon and esophageal cancers; **x)** co-developing the "BAD" technology for molecular early detection of progression of Barrett's esophagus (BE) toward cancer by applying next generation sequencing to detect nascent BE clones bearing "progression-driver" chromosome aberrations. Markowitz has moreover spearheaded the clinical translation of multiple of these groundbreaking laboratory discoveries. Examples include: **i)** Founding Rodeo Therapeutics for preclinical development of 15-PGDH inhibitors as therapeutics for tissue regeneration and repair (with acquisition in 2021 by Amgen); **ii)** FDA approval of Markowitz's esophageal sampling device plus FDA breakthrough device designation of Markowitz's methylated DNA assay for detecting Barrett's, with commercialization of these technologies (EsoCheck and EsoGuard) by Lucid Diagnostics; **iii)** common clinical adoption of Markowitz's assay of hMLH1 methylation for distinguishing DNA mismatch repair deficient colon cancers as being either Lynch syndrome or sporadic in origin. Recent examples of impactful discovery are Markowitz's 2015 publication in Science on 15-PGDH inhibition for potentiating tissue repair (ref. 4a), his 2018 Science Translational Medicine paper on developing non-endoscopic biomarker based early detection of esophageal neoplasias (ref 5c), and his 2025 PNAS paper on 15-PGDH inhibition therapy for blocking neurodegeneration in Alzheimer's disease and after traumatic brain injury (ref 4d). Markowitz's national recognitions include serving on the NCI Board of Scientific Counselors; serving on the External Advisory Boards of multiple major cancer centers; authoring invited editorials/reviews in major medical and scientific journals (e.g 1-3 below); and his being named an NCI Outstanding Investigator (2016-2023) and the Principal Investigator of the Case GI SPORE (2011-2023).

1. Markowitz SD, Bertagnolli MM. (2009). Molecular basis of colorectal cancer. N Engl J Med, 361(25), 2449-

60. PMCID: PMC2843693.
2. Markowitz SD. (2007) Aspirin and colon cancer-targeting prevention? N Engl J Med, 356(21), 2195-8.
3. Markowitz SD. (2017) Cancer bypasses the lymph nodes. Science. 357(6346):35-6.

Ongoing and recently completed projects that I would like to highlight include:
NIH R01CA295877 S. Markowitz, Contact P.I. (MPI: Markowitz, Chak, Willis) 01/03/2025–12/31/2029
A Clinical Trial of Cancer Prevention by Biomarker Based Detections of Barrett's Esophagus and Its Progression.

NIH U01 CA271867 S. Markowitz, Contact P.I. (MPI: Markowitz, Chak, Willis, others) 9/21/22-8/31/27
Early Detection Research Network: Validation of Biomarkers for Predicting Barrett's Esophagus Progression.

NIH RM1GM142002 S. Markowitz, MPI 6/1/21–05/31/26
Chemical, Structural and Cell-Signaling Interrogation of 15-Prostanglandin Dehydrogenase in Tissue Repair and Regeneration.

NIH R35 CA197442 S. Markowitz, P.I. NCI Outstanding Investigator Award 12/1/16-11/30/23
Targeting 15-Prostaglandin Dehydrogenase (15- PGDH) in Cancer Risk, Prevention, and Treatment.

B. Positions, Scientific Appointments, and Honors

Positions

2015- Distinguished University Professor, Case Western Reserve University
1997- Markowitz-Ingalls Professor of Cancer Genetics, Medicine-Hematology/Oncology, Case Western Reserve University and University Hospitals Seidman Cancer Center, Cleveland, OH
1998-2010 Investigator, Howard Hughes Medical Institute
1995-2021 Co-Leader, Cancer Genetics Program, Case Comprehensive Cancer Center, Cleveland, OH
1987-1997 Assistant/Associate Professor, Medicine-Hematology/Oncology, Case Western Reserve University and University Hospitals Cleveland, Cleveland, OH
1984-1987 Fellow, NCI Clinical Oncology Program, & Postdoctoral research, Molecular Biology Laboratory, NCI-Navy-M.O.B., Dr. John Minna, Branch Chief
1981-1984 Resident in Internal Medicine, University of Chicago Hospitals & Clinics
1977-1980 M.D.-Ph.D. graduate student with Dr. V. T. Marchesi, Yale University, New Haven, CT

Selected Honors and Awards

Honorary Societies: (2005) American Association Physicians; (1995) American Society Clinical Investigation.
Selected Awards // Honorary Lectureships: 2025 Cozzarelli Prize for PNAS "Paper of Year" in Biomedical Sciences; (2016) NCI Outstanding Investigator; (2016) Hamdan Award for Medical Research Excellence (Dubai); (2016) Clinical Research Forum "Top 10" Award; (2013) Scholar Innovator Award, Harrington Discovery Institute; (2011) Sadie Gerson Distinguished Scholar Award, University of Pittsburgh; (2000) Ohio State University Cancer Genetics Medal; // (2017) Wadler Visiting Professor, Weill Cornell Medical College; (2009) Baldini Visiting Professor, Harvard Medical School; (2007 & 1998) Lecturer Princess Takamatsu Cancer Research Fund, Tokyo, Japan; (2000) Petros Palandjian Visiting Professor, Harvard Medical School.

Selected Committees

2021: Member, NIH SPORE Review Study Section, ZCA1 RPRB-7 (M1) S
2019-2020: Chair, External Steering Panel, NCI PREVENT Cancer Program;
2011- 2016: National Cancer Institute: Board of Scientific Counselors-Clinical Sciences and Epidemiology;
Selected EABs: Memorial Sloan Kettering Cancer Center-Human Oncology and Pathogenesis Program (2007-present); Dana Farber-Harvard Comprehensive Cancer Center (2006-2012); University of Pennsylvania Abramson Cancer Research Institute (1999-2007); National Colorectal Cancer Research Alliance (1999-2016).

Selected Inventions (out of 39 awarded U.S. patents)

i. Methods and Compositions For Detecting Cancers Associated With Methylation of HMLH1 Promoter DNA; U.S. Patent 8669060. (Method in clinical use for detecting MLH1 methylated colon cancers.)
ii. Methods and Compositions for Detecting Colon Cancers; U.S. Patent 7485420 (Commercialized by Exact Sciences and LabCorp as "ColoSure" stool DNA test for early detection of colorectal cancers.)
iii. Methods and Compositions for Detecting Gastrointestinal and Other Cancers; U.S. Patent 9580754. (Commercialized by Lucid Diagnostics as the "EsoGuard" test for detection of Barrett's esophagus. Awarded FDA Breakthrough Device Designation, 2020.)
iv. Device for Collecting a Biological Sample; US Patent 10660621. (Commercialized by Lucid Diagnostics as the EsoCheck Device for non-endoscopic esophageal sampling. FDA approved 2020.
v. Compositions and Methods of Modulating 15-PGDH Activity, U.S. Patent 9790233. (Licensed to Rodeo Therapeutics [now Amgen] for clinical development of 15-PGDH inhibitor drugs as tissue regeneration agents.)

C. Contributions to Science

My work has had major impact on elucidating fundamental aspects of the genetics of gastrointestinal cancers and on the translation of cancer genetics discoveries for medical application. Five specific areas of impact are:

1. Discovering mutations in TGF-ß RII receptors. My laboratory made the first discovery that TGF-ß receptors are tumor suppressor genes and are targets for mutational inactivation in human cancers. We first discovered that biallelic inactivating TGF-ß RII (TGBR2) frameshift mutations are ubiquitous in colon cancers with microsatellite instability (MSI) (1a). MSI is the phenotypic hallmark of colon cancers defective in DNA mismatch repair (MMR), notably including Lynch Syndrome cancers in which MMR defects are inherited. I discovered that MSI colon cancers universally activate a 10bp polyadenine TGFBR2 coding sequence as a hotspot for frameshift mutations. This discovery had two major implications. First, it provided the first genetic proof that the TGF-ß pathway is a colon cancer suppressor. Second, it provided the molecular mechanism explaining how and why individuals with Lynch syndrome (and MMR defects) develop colon cancer – via hyper-accelerated mutational targeting of TGFBR2. I next showed TGFBR2 mutations are also highly common in MSI gastric cancers, but are absent in MSI endometrial cancers (1b), i.e. TGFBR2 mutations are specifically selected for in cancers of the GI tract. I extended this discovery by showing that TGFBR2 is also targeted for inactivating mutations (mostly kinase domain) in non-MSI (MSS) colon cancers (1c), with TGFBR2 mutations cumulatively present in one-third of all colon cancers. In additional collaborative studies, I further showed that colon cancers with wild-type TGFBR2 commonly bear inactivating mutations in SMAD genes, which encode key downstream elements of TGF-ß signaling. Major validation of this work emerged from my participation as a key member of the team that sequenced the colon cancer exome (1d), the first full cancer exome to be sequenced, that again found TGFBRII and SMADs are both significantly mutated driver genes in colon cancer. Mutational inactivation of the TGF-ß pathway is now recognized as a hallmark of gastrointestinal cancers, including colon, gastric, and pancreatic cancers, with the seminal discovery of this tumor suppressor pathway arising directly from my work.

1a. Markowitz S*, Wang J, Myeroff L, Parsons R, Sun L, Lutterbaugh J, Fan RS, Zborowska E, Kinzler KW, Vogelstein B, Brattain M, Willson JKV. (1995). Inactivation of type II TGFß receptor in colon cancer cells with microsatellite instability. Science 268, 1336-1338. (*SM corresponding author).

1b. Myeroff L, Parsons R, Kim S-J, Hedrick L, Cho K, Orth K, Mathis M, Kinzler K, Lutterbaugh J, Park K, Bang Y-J, Lee HY, Park J-G, Lynch H, Roberts A, Vogelstein B, Markowitz S. (1995). A TGF-beta receptor type II gene mutation common in colon and gastric but rare in endometrial cancers with microsatellite instability. Cancer Res 55, 5545-7.

1c. Grady W, Myeroff L, Swinler S, Rajput A, Thiagalingam S, Lutterbaugh J, Neumann A, Brattain M, Chang J, Kim S-J, Kinzler K, Vogelstein B, Willson J, Markowitz S. (1999). Mutational inactivation of transforming growth factor ß recepor type II in microsatellite stable colon cancers. Cancer Res. 59,320-4.

1d. Wood LD, Parsons D, Jones S, Lin J, Sjoblom T, Leary RJ, Shen D, Boca SM, Barber T, Ptak J, Silliman N, Szabo S, Dezso Z, Ustyanksky V, Nikolskaya T, Nikolsky Y, Karchin R, Wilson PA, Kaminker J, Zhang Z, Croshaw R, Willis J, Dawson D, Shipitsin M, Willson JK, Sukumar S, Polyak K, Park BH, Pethiyagoda C, Pant P, Ballinger D, Sparks A, Hartigan J, Smith DR, Suh E, Papadopoulos N, Buckhaults P, Markowitz SD, Parmigiani G, Kinzler K, Velculescu VE, Vogelstein B. (2007). The genomic landscapes of human breast and colorectal cancers. Science 318, 1108-1113.

2. Identifying 15-PGDH as a colon cancer suppressor and TGF-ß effector. My laboratory has maintained an abiding interest in identifying how TGF-ß acts as a potent suppressor of GI cancers. Genome-wide expression profiling to identify transcripts that TGF-ß turns on, but that colon cancers turn off, identified 15-Prostaglandin Dehydrogenase (15-PGDH, gene name HPGD) as the best such exemplar (2a). 15-PGDH is a prostaglandin degrading enzyme that had not previously been linked to cancer. In short order my lab demonstrated: i) 15-PGDH protein is highly induced by TGF-ß, is highly expressed by normal colonocytes, and is turned off in 85% of colon cancers (2a); ii) 15-PGDH is a COX-2 metabolic antagonist that lowers PGE2 in tissues (2b); iii) restoring 15-PGDH expression blocks colon cancers ability to form tumors in athymic mice (2a); and iv) knocking out 15-PGDH accelerates induction of murine colon tumors by 7-fold (2b). I have further associated 15-PGDH pathway defects with increased colon cancer risk by identifying a family in which germline inactivating mutations in SLCO2A1, that encodes the prostaglandin transporter (PGT) that brings substrate to 15-PGDH, are associated with early onset of colon cancers and adenomas (2c). These findings confirmed that: i) 15-PGDH is a key effector of TGF-ß's suppression of tissue growth; ii) 15-PGDH is a tumor suppressor whose inactivation is a key step in human colon carcinogenesis; iii) PGE2 is an oncometabolite; iv) TGF-ß suppression of GI cancers is mediated in part by metabolic antagonism of oncogenic COX-2.

2a. Yan M, Rerko RM, Platzer P, Dawson D, Willis J, Tong M, Lawrence E, Lutterbaugh J, Lu S, Willson JK, Luo G, Hensold J, Tai HH, Wilson K, Markowitz SD. (2004). 15-Hydroxyprostaglandin dehydrogenase, a COX-2 oncogene antagonist, is a TGF-beta-induced suppressor of human gastrointestinal cancers. Proc Natl Acad Sci USA. 101, 17468-17473. PMCID: PMC536023 (Selected as "From the Cover" article)

2b. Myung SJ, Rerko RM, Yan M, Platzer P, Guda K, Dotson A, Lawrence E, Dannenberg AJ, Lovgren AK, Luo G, Pretlow TP, Newman RA, Willis J, Dawson D, Markowitz SD. (2006). 15-Hydroxyprostaglandin dehydrogenase is an *in vivo* suppressor of colon tumorigenesis. Proc Natl Acad Sci USA.

103, 12098-12102. PMCID: PMC1567703
2c. Guda K, Fink SP, Milne GL, Molyneaux N, Ravi L, Lewis SM, Dannenberg AJ, Montgomery CG, Zhang S, Willis J, Wiesner GL, Markowitz SD. (2014). Inactivating Mutation in the Prostaglandin Transporter Gene, SLCO2A1, Associated with Familial Digital Clubbing, Colon Neoplasia, and NSAID Resistance. Cancer Prev Res (Phila). 7(8), 805-12. PMCID: PMC4125515 (Selected as "AACR Editors' Pick article).

3. Discovering 15-PGDH is a negative regulator of stem cell response to tissue injury in the colon, liver, and other organs. And furthermore, developing the first in vivo active small molecule 15-PGDH inhibitors as therapeutic agents for tissue regeneration and repair. We provided major insight into the biological mechanism of 15-PGDH tumor suppression in studies published in Science in 2015, in which we showed that in multiple tissues, loss of 15-PGDH markedly potentiates the proliferative response of tissue stem cells following tissue injury (3a). Thus, DSS induces crypt injury and colon ulceration in 15-PGDH wild-type mice. However, in 15-PGDH knockout mice, DSS instead induces a marked increase in DNA synthesis and proliferation of cells at the base of the colon crypts, which completely prevents any crypt damage or mucosal ulceration (3a). We showed similar responses in the liver, where after partial hepatectomy, 15-PGDH knockout mice double rates of both BrdU incorporation and liver regrowth (3a). And we showed similar effects in the bone marrow, where inhibiting 15-PGDH markedly accelerates hematopoietic recovery after a bone marrow transplant (3a). Tumor suppression by 15-PGDH is thus intimately related to regulation of tissue stem cell responses to injury, leading to a model where optimal medicinal regulation of 15-PGDH would be to maintain chronic high basal 15-PGDH expression to favor tumor prevention, but to be able to acutely turn off 15-PGDH for short periods in settings of acute organ injury (e.g. after liver surgery or bone marrow transplant). To identify 15-PGDH modulators that could advance these translational goals, we performed a cell-based screen of 230,000 small molecules. This screen identified a lead 15-PGDH inhibitor, SW033291 (Ki=0.1nM) that: protects the colon from colitis; accelerates liver regeneration after liver surgery; and accelerates bone marrow regeneration after bone marrow transplantation (3a). We are bringing optimized versions of this inhibitor (3b) forward for clinical development together with Amgen, that in 2021 acquired Rodeo Therapeutics, the biotechnology startup that I founded for preclinical development of this technology. We are further advancing translation of this technology through development of an orally bioavailable series of 15-PGDH inhibitors on a new and distinct chemical scaffold (3c). Most recently, we have advanced this science by solving at atomic resolution the cryo-EM structure of 15-PGDH when complexed to both the inhibitor series, identifying a dynamic "Pac-Man" like 15-PGDH domain that we show swallows physiologic 15-PGDH substrates (e.g. PGE2) and then releases enzymatic reaction products (e.g. 15-keto-PGE2), but that upon swallowing our inhibitors becomes permanently locked in the closed position (3d).

3a. Zhang Y, Desai A, Yang SY, Bae KB, Antczak MI, Fink SP, Tiwari S, Willis JE, Williams NS, Dawson DM, Wald D, Chen WD, Wang Z, Kasturi L, Larusch GA, He L, Cominelli F, Di Martino L, Djuric Z, Milne GL, Chance M, Sanabria J, Dealwis C, Mikkola D, Naidoo J, Wei S, Tai HH, Gerson SL, Ready JM, Posner B, Willson JK, Markowitz SD. (2015). Inhibition of the prostaglandin-degrading enzyme 15-PGDH potentiates tissue regeneration. Science. 348(6240):aaa2340. PMCID: PMC4481126
3b. Antczak MI, Zhang Y, Wang C, Doran J, Naidoo J, Voruganti S, Williams NS, Markowitz SD*, Ready JM*. (2017). Inhibitors of 15-Prostaglandin Dehydrogenase To Potentiate Tissue Repair. J Med Chem. 60(9):3979-4001. PMCID: PMC5580352. (*SDM, JMR co-corresponding authors)
3c. Hu B, Toda K, Wang X, Antczak MI, Smith J, Geboers S, Nishikawa G, Li H, Dawson D, Fink S, Desai AB, Williams NS, Markowitz SD*, Ready JM*. Orally Bioavailable Quinoxaline Inhibitors of 15-Prostaglandin Dehydrogenase (15-PGDH) Promote Tissue Repair and Regeneration (2022). J Med Chem. 65(22):15327-43. PMCID: PMC9885488 (* SDM and JMR co-corresponding authors)
3d. Huang W, Li H, Kiselar J, Fink SP, Regmi S, Day A, Yuan Y, Chance M, Ready JM*, Markowitz SD*, Taylor DJ*. (2023). Small molecule inhibitors of 15-PGDH exploit a physiologic induced-fit closing system. Nat Commun.14(1):784. PMCID: PMC9922282 (*JR, SDM, DT co-corresponding authors)

4. Demonstrating therapeutic tissue regeneration and anti-inflammatory activity of 15-PGDH inhibition in added murine disease models that span bone marrow injury (4a,4b), lung fibrosis (4c), Alzheimer's disease and traumatic brain injury (4d). With Drs. Desai and Pieper, we have advanced regenerative medicine application of 15-PGDH inhibitors by interrogating mechanism and showing generality of activity in: i) potentiating hematopoietic recovery after bone marrow transplant (4a, 4b); ii) catalyzing lung recovery in murine models of pulmonary fibrosis, a lethal disease in humans (4c); and iii) completely protecting from neurodegeneration in murine models of Alzheimer's disease and traumatic brain injury, via a novel further mechanism of 15-PGDH inhibition blocking macrophage/microglial generation of reactive oxygen species (4d).

4a. Desai A, Zhang Y, Park Y, Dawson DM, Larusch GA, Kasturi L, Wald D, Ready JM, Gerson SL, Markowitz SD. (2018). A second-generation 15-PGDH inhibitor promotes bone marrow transplant recovery independent of age, transplant dose, and G-CSF support. Haematologica. 103(6):1054-64. PMCID: PMC6058768
4b. Smith JN, Dawson DM, Christo KF, Jogasuria AP, Cameron MJ, Antczak MI, Ready JM, Gerson SL, Markowitz SD, Desai AB. (2021). 15-PGDH inhibition activates the splenic niche to promote hematopoietic regeneration. JCI Insight. 6(6). PMCID: PMC8026178.

4c. Smith JNP, Witkin MD, Jogasuria AP, Christo KF, Raffay TM, Markowitz SD*, Desai AB*. (2020). Therapeutic targeting of 15-PGDH in murine pulmonary fibrosis. Sci Rep.10(1):11657. PMCID: PMC7363833. (*SDM and ABD co-corresponding authors)

4d. Koh Y, Vázquez-Rosa E, Gao F, Li H, Chakraborty S, Tripathi SJ, Barker S, Bud Z, Bangalore A, Kandjoze UP, León-Alvarado RA, Sridharan PS, Cordova BA, Yu Y, Hyung J, Fang H, Singh S, Katabathula R, LaFramboise T, Kasturi L, Lutterbaugh J, Beard L, Cordova E, Cintrón-Pérez CJ, Franke K, Franco Fragoso MF, Miller E, Indrakumar V, Noel KL, Dhar M, Ajroud K, Zamudio C, Lopes FBTP, Bambakidis E, Zhu X, Wilson B, Flanagan ME, Gefen T, Fujioka H, Fink SP, Desai AB, Dawson D, Williams NS, Kim YK, Ready JM, Paul BD, Shin MK*, Markowitz SD*, Pieper AA*. (2025). Inhibiting 15-PGDH blocks blood-brain barrier deterioration and protects mice from Alzheimer's disease and traumatic brain injury. Proc Natl Acad Sci USA. 2025;122(21):e2417224122. PMCID: PMC12130856. (*SDM, MKS, AAP co-corresponding authors)(Highlighted by co-published PNAS Commentary)

5. Identifying aberrant DNA methylation and aberrant chromosomes as mediators of GI cancers and as biomarkers for early neoplasia detection. In Lynch syndrome, inherited DNA mismatch repair (MMR) gene defects give rise to MMR deficient microsatellite unstable (MSI) type colon cancers, but the basis of common non-familial MSI colon cancers was a mystery. My laboratory was one of 3 groups that co-discovered that non-familial MSI colon cancers arise due to aberrant methylation and transcriptional silencing of the hMHL1 MMR gene (5a). My assay for detecting hMLH1 methylation has been widely adopted for clinical use in distinguishing sporadic from inherited MSI colon cancers. We again identified aberrant methylation as a cancer driver by subsequently discovering aberrant promoter methylation and silencing of the CDH1 gene is the frequent second hit in development of Hereditary Diffuse Gastric Cancers, arising in persons who inherit a germline mutant CDH1 allele. In translational studies, my group then conducted among the first genome-wide screens for discovering loci aberrantly methylated in GI cancers. We discovered Vimentin exon-1 as targeted for aberrant methylation (mVIM) in 83% of colon cancers, with 1000-fold higher methylation in cancers than in normal colon (5b). We developed a sensitive methylation specific PCR assay for detecting mVIM in DNA from stools (5b), that in a clinical trial successfully detected 84% of early stage colon cancer cases. This conceptual and technological breakthrough led to the first non-invasive test for colon cancer, based on detecting aberrantly methylated DNA in stool, with mVIM testing of stool DNA commercialized by Exact Sciences and LabCorp for clinical use as ColoSure®. Based on this foundational innovation, Exact Sciences developed the follow-on ColoGuard® test of methylated stool DNA, FDA approved in 2014, and marking the successful translation of an idea originated by my laboratory into now widespread clinical use. Moreover, my group has further shown that mVIM has an even greater, 90% sensitivity, for detecting esophageal cancers and their precursor lesion, Barrett's esophagus (BE) (5c). We validated this approach in a clinical trial in which an mVIM anchored DNA panel showed >90% sensitivity and specificity for BE detection in esophagus samples that were obtained via a novel swallowable balloon-based device that our team also developed (5c). This discovery creates a practical method for simple non-endoscopic early detection of BE and early esophagus cancers, with the balloon device now FDA approved, the methylated DNA panel granted FDA breakthrough device designation, and the combined technologies commercialized by Lucid Diagnostics as EsoCheck and EsoGuard, respectively. We have extended this work by developing a novel technology, "BAD", that detects early progression of BE to dysplasia or cancer, by applying DNA sequencing-based liquid biopsy technology (from the Vogelstein lab) to analysis of esophageal brushings, thus sensitively detecting DNA read imbalances indicative of nascent BE clones that have acquired structural alterations (regional gains and losses) on specific "driver chromosomes" that typify clonal progression toward cancer (5d).

5a. Veigl M, Kasturi L, Olechnowicz J, Ma A, Lutterbaugh J, Periyasamy S, Li G-M, Drummond J, Modrich P, Sedwick WD, Markowitz S. (1998). Biallelic Inactivation of hMLH1 by Epigenetic Gene Silencing, A Novel Mechanism Causing Human MSI Cancers. Proc Natl Acad Sci USA. 195, 8698-702.

5b. Chen WD, Han ZJ, Skoletsky J, Olson J, Sah J, Myeroff L, Platzer P, Lu S, Dawson D, Willis J, Pretlow TP, Lutterbaugh J, Kasturi L, Willson JK, Rao JS, Shuber A, Markowitz SD. (2005). Detection in fecal DNA of colon cancer-specific methylation of the nonexpressed vimentin gene. J Natl Cancer Inst 97, 1124-1132.

5c. Moinova HR, LaFramboise T, Lutterbaugh JD, Chandar AK, Dumot J, Faulx A, Brock W, Cabrera ODL, Guda K, Barnholtz-Sloan J, Iyear PG, Canto MI, Wang JS, Shaheen NJ, Thota PN, Willis JE, Chak A, Markowitz SD. (2018). Identifying DNA Methylation Biomarkers for Non-Endoscopic Detection of Barrett's Esophagus. Science Translational Medicine. 10(424):eaao5848. PMCID: PMC5789768.

5d. Douville C[#], Moinova HR[#], Thota PN, Shaheen NJ, Iyer PG, Canto MI, Wang JS, Dumot JA, Faulx A, Kinzler KW, Papadopoulos N, Vogelstein B, Markowitz SD*, Bettegowda C, Willis JE, Chak A.* (2021). Massively Parallel Sequencing of Esophageal Brushings Enables an Aneuploidy-Based Classification of Patients With Barrett's Esophagus. Gastroenterology. 160(6):2043-54 e2. PMCID: PMC8141353. (authors: *SDM and AC co-corresponding authors; [#]HM (SDM lab) co-first author)

Complete List of Published Work in MyBibliography:
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