RESEARCH BEING DONE USING GCRF FUNDS

The overarching goal of the Chi Lab is to understand GIST development and pathogenesis, build clinically relevant disease models, and develop new therapeutic strategies with the potential to improve and ultimately transform patient care. Our work focuses on the key lineage-regulatory proteins ETV1 and FOXF1, which are critical for GIST cell survival and disease biology. A major focus has been therapeutic targeting of ETV1 through combined KIT and MEK inhibition. This strategy has been evaluated in a clinical trial of imatinib plus binimetinib in advanced GIST, demonstrating promising safety and efficacy results that support further clinical development. Building on these findings, we are advancing a randomized Alliance phase II trial evaluating imatinib in combination with MEK/FAK pathway inhibition in the frontline treatment of advanced GIST. In parallel, our laboratory is developing new approaches to target FOXF1, an upstream regulator of both KIT and ETV1, and is investigating the broader GIST ecosystem, including how tumor-intrinsic programs, stromal interactions, vasculature, and metastatic niches contribute to disease progression, liver and peritoneal metastasis, and therapeutic resistance.

PROGRESS REPORT

Clinical Trial: With GCAF support, we completed the phase Ib/II clinical trial of imatinib plus binimetinib in advanced GIST (IRB#13-162, NCT01991379). The phase Ib portion established the recommended phase II dose and demonstrated that the combination was safe and manageable. Although limited activity was observed in imatinib-refractory KIT/PDGFRA-mutant GIST, encouraging clinical benefit was seen in SDH-deficient GIST, including a confirmed partial response and durable benefit in one patient. These findings were published in Clinical Cancer Research (2022) and support further evaluation of this combination strategy in SDH-deficient GIST.

The phase II portion evaluated imatinib plus binimetinib as first-line therapy for advanced GIST. The study met its primary endpoint, with a RECIST1.1 objective response rate of 69.0% and median progression-free survival of 29.9 months. Several patients with locally advanced disease were able to undergo surgery after treatment, with substantial pathological response. These results, published in Journal of Clinical Oncology (2022), provide proof-of-principle that targeting GIST lineage dependency through combined KIT and MEK inhibition can enhance clinical efficacy. A 10-year follow up manuscript has been submitted, under review currently.

Based on these clinical and preclinical observations, we are now advancing a randomized Alliance phase II trial comparing imatinib plus MEK/FAK pathway inhibition versus imatinib alone in the frontline treatment of advanced GIST. We have secured drug supply commitment from Verastem Oncology for avutometinib and defactinib, and the trial is currently undergoing review through NCI/CTEP/Alliance committees.

Building relevant models for GIST with high risk molecular features (e.g., MAX/MGA mutations) and therapeutic-resistant GIST: Our laboratory has also made significant progress in developing clinically relevant GIST models. We have established and validated more than 10 patient-derived xenograft models of therapeutic-resistant GIST, including models resistant to imatinib, sunitinib, regorafenib, and ripretinib. These models are now available for mechanistic and therapeutic studies. In addition, we developed a GIST liver metastasis model using engineered MAX-deficient GIST T1 cells, which recapitulates high-risk metastatic behavior and is being used to identify mechanisms of liver metastasis and potential therapeutic vulnerabilities.

Evaluation of cfDNA samples: In collaboration with Ciara Kelly, we have collected serial cfDNA samples from patients receiving imatinib plus binimetinib and other standard GIST therapies, including imatinib, sunitinib, regorafenib, and ripretinib. These samples are being analyzed through MSK-ACCESS to define genetic mechanisms of therapeutic resistance and guide future strategies to overcome disease progression.

FACILITIES:

Trained as a physician-scientist, I recently joined the faculty of MSKCC with a primary appointment in the Human Oncology and Pathogenesis Program (HOPP) and a joint appointment on the Sarcoma Oncology service, Department of Medicine. HOPP, chaired by Charles Sawyers, is a relatively new laboratory-based research program at MSKCC, established to create a highly interactive group of outstanding physician-scientists across clinical disciplines all conducting translational research. The mission of HOPP is to bring such individuals together under one roof and provide the resources and infrastructure required to translate molecular insights into clinical trials. Sarcoma oncology service led by Dr. William D. Tap currently has 6 clinical investigators including myself, conducting multiple clinical trials, in particular a large number of Phase I/II trials. My clinical activities involve half a day a week in clinic taking care of melanoma and sarcoma patients and participate in clinical trials, and 3 weeks of inpatient service time per year. The rest of my time is mainly devoted to clinically relevant mechanistic and translational laboratory research with a focus in GIST/sarcoma and melanoma.

HOPP is a highly interactive program that interfaces with the more basic research-oriented Sloan-Kettering Institute (SKI) and the clinically-oriented Memorial Hospital. Currently there are 20 HOPP faculties whose clinical backgrounds include medical oncology, pathology, neurology, radiation oncology and endocrinology. It provides me with an ideal translational environment where I can focus on my research in the laboratory and retain close links to the clinic through participation in the relevant disease management teams. HOPP currently occupies three floors in the Zuckerman Research Center. This 23-story building also houses MSKCC's five "bridge" programs whose faculties share common interests in transcriptional regulation, cancer biology and genetics, chromatin biology and cancer epigenetics, cancer genomics, and therapeutic development. In addition to HOPP, these include Cancer Biology and Genetics (CBG) directed by Dr. Massagué (now director of SKI), Pharmacology directed by Dr. Scheinberg, Immunology directed by Dr. Rudensky and Computational Biology Center headed by Dr. Sander. HOPP has a weekly "work in progress" for faculties and joint weekly Science Clubs with CBG where postdocs and graduate students present unpublished work. There are numerous forums for invited speakers including weekly MSKCC "presidential seminars", HOPP research seminar series, SKI special seminars, and research seminars in the neighboring Weill Cornell Medical College and The Rockefeller University. I interact regularly with other MSKCC faculties including Drs. William Tap (sarcoma oncology), Christina Antonescu (pathology), Neal Rosen (oncology/pharmacology), Yu Chen (HOPP) and Charles Sawyers (HOPP). In addition, HOPP is just across the street from Cornell Weill Medical College and two blocks away from the Rockefeller University where I did my MD/PhD and postdoctoral training. The familiarity and close vicinity of the tri-institutional scientific environment have made it very easy for me to establish collaborations. HOPP has also developed a structured mentoring program as further commitment to career development for junior faculties. There is also a career development series for young women faculty members at MSKCC. All of these will be critical for a successful scientific career development in the future.

My lab is located on the 5th floor of ZRC, occupying 2 full bays with bench and desk spaces for 8 researchers, with the potential to expand as needed. My laboratory is fully equipped for standard molecular biology, tissue culture (3 hoods, 4 incubators), gene transfer, biochemistry, genomics, epigenetics/epigenomics and mouse modeling experiments. HOPP operates on open lab space with many core equipments include ultracentrifuges, scintillation counter, HPLC/FPLC, PCR and real-time PCR machines, ELISA plate reader, incubator shakers, Bioruptor machines, gel dryer, isoflurane vaporizer, fluorescence upright and inverted microscopes, gel-imaging systems, and gel-documentation systems, Vicell cell counters, one spectrophotometer, liquid nitrogen freezers, autoclave machines, FACS etc. Moreover, we have full access to the genomics resource core at both MSKCC and RU with established services for genotyping, microarray, and high-throughput deep sequencing (HiSeq), which will be critical for RNA-seq, Whole exome sequencing (WES) and ChIP-seq of chromatin marks and transcription factors. I also have easy access to liquid handlers, many 384 well PCR machines, genome-wide and custom RNAi libraries, as well as robotic based and custom-built screening platforms and data management in the Geoffrey Beene Translational Oncology Core Facility and the High-Throughput Screening Core Facility located on the 6th and 19th floors of Zuckerman respectively. The mouse facilities with ample space are located at the basements of the ZRC and we readily have access to the mouse core tissue facilities in ZRC. We are well experienced to perform the basic level of ChIP-seq, RNA-seq and WES analyses and the MSKCC bioinfomatics core assistance is readily available to us. We will work closely with the Sarcoma Oncology clinical investigators for expedited clinical translation of laboratory findings for novel therapeutic.

OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Chi, Ping

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-0159-5531

Position Title: Member (with Tenure)

Organization and Location: Human Oncology and Pathogenesis Program (HOPP), Memorial Sloan Kettering Cancer Center, New York, New York, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
The Rockefeller University (Concurrent with Clinical Fellowship), New York, NY, United States	Postdoctoral Fellow	07/2006	08/2011	Chromatin Biology & Epigenetics
Memorial Sloan Kettering Cancer Center, New York, NY, United States	Fellow	07/2005	08/2011	Hematology and Oncology (Clinical)
Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States	Resident	07/2003	06/2005	Internal Medicine
The Rockefeller University (Part of the Tri-Institutional MSTP program), New York, NY, United States	DOCTOR OF PHILOSOPHY	07/1998	11/2001	Molecular & Cellular Neuroscience
Weill Medical College of Cornell University, New York, NY, United States	DOCTOR OF MEDICINE	07/1996	06/2003	Medicine (Part of the Tri-Institutional MD/PhD Program)
Mount Holyoke College, South Hadley, MA, United States	BACHELOR OF ARTS	09/1992	06/1996	Biochemistry

Appointments and Positions

2023 - present	Member (with Tenure), Human Oncology and Pathogenesis Program (HOPP), Memorial Sloan Kettering Cancer Center, New York, New York, United States
2024 - present	Co-Director, Translational Research, MSK Sarcoma Center, New York, NY, United States
2023 - present	Attending Physician, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases, New York, NY, United Statess
2023 - present	Professor of Medicine (with Tenure), Weill Cornell Medical College, New York, NY, United States
2023 - 2023	Ad hoc member, DOD Peer Review Committee, FY23 NFRP for the DOD CDMRP, Washington DC, District of Columbia, United States
2023 - 2023	Ad hoc member, NCATS Peer Review Committee, Rare Disease Study Section, Washington DC, District of Columbia, United States
2023 - 2023	Ad hoc member, NIH Peer Review Committee, MCTA Study Section, Washington DC, District of Columbia, United States
2022 - present	Chartered Member, NIH Peer Review Committee, New Innovator Award Program (DP2), Washington DC, District of Columbia, United States
2018 - 2023	Associate Professor of Medicine, Weill Cornell Medical College, New York, NY, United States
2018 - 2023	Associate Attending Physician , Department of Medicine, Memorial Hospital for Cancer and Allied Diseases, New York, NY, United States
2018 - 2023	Associate Member, Human Oncology and Pathogenesis Program (HOPP), Memorial Sloan Kettering Cancer Center, New York, NY, United States
2017 - present	Elected Membership, American Society of Clinical Investigation (ASCI), Ann Arbor, Michigan, United States
2012 - present	Member, Connective Tissue Oncology Society, Alexandria, Virginia, United States

2012 - 2018	Assistant Professor of Medicine, Weill Cornell Medical College, New York, NY, United States
2011 - 2018	Assistant Attending Physician, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases, New York, NY, United States
2011 - 2018	Assistant Member, Human Oncology (HOPP), Memorial Sloan Kettering Cancer Center, New York, NY, United States
2006 - present	Member, American Association of Cancer Research, Philadelphia, Pennsylvania, United States
2006 - present	Member, American Society of Clinical Oncology, Alexandria, Pennsylvania, United States

Products

Products Closely Related to the Proposed Project

1. Lee W, Teckie S, Wiesner T, Ran L, Prieto Granada CN, Lin M, Zhu S, Cao Z, Liang Y, Sboner A, Tap WD, Fletcher JA, Huberman KH, Qin LX, Viale A, Singer S, Zheng D, Berger MF, Chen Y, Antonescu CR, Chi P. PRC2 is recurrently inactivated through EED or SUZ12 loss in malignant peripheral nerve sheath tumors. Nat Genet. 2014 Nov;46(11):1227-32. PubMed Central PMCID: PMC4249650.
2. Prieto-Granada CN, Wiesner T, Messina JL, Jungbluth AA, Chi P, Antonescu CR. Loss of H3K27me3 Expression Is a Highly Sensitive Marker for Sporadic and Radiation-induced MPNST. Am J Surg Pathol. 2016 Apr;40(4):479-89. PubMed Central PMCID: PMC4882106.
3. Miranda-Román MA, Lee CJ, Fishinevich E, Ran L, Patel AJ, Yan J, Khudoynazarova MN, Warda S, Pachai MR, Chen Y, Chi P. MEK Inhibitors Lead to PDGFR Pathway Upregulation and Sensitize Tumors to RAF Dimer Inhibitors in NF1-Deficient Malignant Peripheral Nerve Sheath Tumor. Clin Cancer Res. 2024 Nov 15;30(22):5154-5165. PubMed Central PMCID: PMC11565172.
4. Patel AJ, Warda S, Maag JLV, Misra R, Miranda-Román MA, Pachai MR, Lee CJ, Li D, Wang N, Bayshtok G, Fishinevich E, Meng Y, Wong EWP, Yan J, Giff E, Pappalardi MB, McCabe MT, Fletcher JA, Rudin CM, Chandarlapaty S, Scandura JM, Koche RP, Glass JL, Antonescu CR, Zheng D, Chen Y, Chi P. PRC2-Inactivating Mutations in Cancer Enhance Cytotoxic Response to DNMT1-Targeted Therapy via Enhanced Viral Mimicry. Cancer Discov. 2022 Sep 2;12(9):2120-2139. PubMed Central PMCID: PMC9437570.
5. Yan J, Chen Y, Patel AJ, Warda S, Lee CJ, Nixon BG, Wong EW, Miranda-Román MA, Yang N, Wang Y, Pachai MR, Sher J, Giff E, Tang F, Khurana E, Singer S, Liu Y, Galbo PM Jr, Maag JL, Koche RP, Zheng D, Antonescu CR, Deng L, Li MO, Chen Y, Chi P. Tumor-intrinsic PRC2 inactivation drives a context-dependent immune-desert microenvironment and is sensitized by immunogenic viruses. J Clin Invest. 2022 Sep 1;132(17) PubMed Central PMCID: PMC9433107.

Other Significant Products Highlighting Contributions to Science

1. Wong EWP, Sahin M, Yang R, Lee U, Li D, Zhan YA, Misra R, Tomas F, Alomran N, Polyzos A, Lee CJ, Trieu T, Martinez-Fundichely A, Wiesner T, Rosowicz A, Cheng S, Liu C, Lallo M, Shoushtari AN, Merghoub T, Hamard PJ, Koche R, Khurana E, Apostolou E, Zheng D, Chen Y, Leslie CS, Chi P. Disruption of TAD hierarchy promotes LTR co-option in cancer. Nat Genet. 2025 Jul;57(7):1754-1765. PubMed Central PMCID: PMC12283374.
2. Wang N, Pachai MR, Li D, Lee CJ, Warda S, Khudoynazarova MN, Cho WH, Xie G, Shah SR, Yao L, Qian C, Wong EWP, Yan J, Tomas FV, Hu W, Kuo F, Gao SP, Luo J, Smith AE, Han M, Gao D, Ge K, Yu H, Chandarlapaty S, Iyer GV, Rosenberg JE, Solit DB, Al-Ahmadie HA, Chi P, Chen Y. Loss of Kmt2c or Kmt2d primes urothelium for tumorigenesis and redistributes KMT2A-menin to bivalent promoters. Nat Genet. 2025 Jan;57(1):165-179. PubMed Central PMCID: PMC11735410.
3. Chi P, Qin LX, Nguyen B, Kelly CM, D'Angelo SP, Dickson MA, Gounder MM, Keohan ML, Movva S, Nacev BA, Rosenbaum E, Thornton KA, Crago AM, Yoon S, Ulaner G, Yeh R, Martindale M, Phelan HT, Biniakewitz MD, Warda S, Lee CJ, Berger MF, Schultz ND, Singer S, Hwang S, Chen Y, Antonescu CR, Tap WD. Phase II Trial of Imatinib Plus Binimetinib in Patients With Treatment-Naive Advanced Gastrointestinal Stromal Tumor. J Clin Oncol. 2022 Mar 20;40(9):997-1008. PubMed Central PMCID: PMC8937014.
4. Ran L, Chen Y, Sher J, Wong EWP, Murphy D, Zhang JQ, Li D, Deniz K, Sirota I, Cao Z, Wang S, Guan Y, Shukla S, Li KY, Chramiec A, Xie Y, Zheng D, Koche RP, Antonescu CR, Chen Y, Chi P. FOXF1 Defines the Core-Regulatory Circuitry in Gastrointestinal Stromal Tumor. Cancer Discov. 2018 Feb;8(2):234-251. PubMed Central PMCID: PMC5809271.
5. Wiesner T, Lee W, Obenauf AC, Ran L, Murali R, Zhang QF, Wong EW, Hu W, Scott SN, Shah RH, Landa I, Button J, Lailler N, Sboner A, Gao D, Murphy DA, Cao Z, Shukla S, Hollmann TJ, Wang L, Borsu L, Merghoub T, Schwartz GK, Postow MA, Ariyan CE, Fagin JA, Zheng D, Ladanyi M, Busam KJ, Berger MF, Chen Y, Chi P. Alternative transcription initiation leads to expression of a novel ALK isoform in cancer. Nature. 2015 Oct 15;526(7573):453-7. PubMed Central PMCID: PMC4807020.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

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Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

Certified by Chi, Ping in SciENcv on 2026-05-28 18:11:44

NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Chi, Ping

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-0159-5531

Position Title: Member (with Tenure)

Organization and Location: Human Oncology and Pathogenesis Program (HOPP), Memorial Sloan Kettering Cancer Center, New York, New York, United States

Personal Statement

I am a NIH-funded physician-scientist who treats patients with sarcoma in the clinic and studies cancer pathogenesis in the laboratory. My laboratory research has focused on the discovery and understanding of novel genetic and epigenetic mechanisms involved in the cellular context/lineage-specific developmental programs and their contribution to cancer pathogenesis. Through mechanistic studies, I aim to identify novel therapeutic strategies to target oncogenic transcription factors and aberrant transcriptional activation of oncogenes, and tumor suppressor loss. I also maintain an active academic clinical practice, lead early phase clinical trials, and work with a multidisciplinary team to care for patients with sarcomas. My laboratory research complements my clinical practice with a focus in epigenetic and transcriptional dysregulation in gastrointestinal stromal tumor (GIST), malignant peripheral nerve sheath tumor (MPNST), angiosarcomas, and other sarcomas.

As a physician-scientist with expertise in transcription regulation, epigenetics, and chromatin biology, combined with my clinical specialization in sarcoma medical oncology, I have dedicated my career to harnessing cutting-edge technologies to drive both mechanistic and therapeutic discoveries in cancer. My goal is to address complex molecular mechanisms underlying cancer pathogenesis and facilitate tailored therapeutic solutions for clinical translation in rare cancers.

Honors

2022	NFRP Investigator-Initiated Research Award, Department of Defense (DOD)
2017	Elected Membership, American Society for Clinical Investigation (ASCI)
2017	Boyer Award in Clinical Research, Memorial Sloan Kettering Cancer Center
2017	Francis S. Collins Scholar Award, Neurofibromatosis Therapeutic Acceleration Program (NTAP)
2015	NFRP New Investigator Award, Department of Defense (DOD)
2014	The ASCI Young Physician-Scientist Award, American Society for Clinical Investigation
2012	NIH Director's New Innovator Award (DP2), National Institute of Health (NIH)
2012	Sidney Kimmel Scholar Award, Sidney Kimmel Foundation
2011	Clinical Scientist Development Award (K08), National Cancer Institute
2008	Young Investigator Award (YIA), American Society of Clinical Oncology (ASCO)
2008	Board Certified in Medical Oncology, Memorial Sloan Kettering Cancer Center
2007	F32 Ruth L. Kirschstein National Research Service Awards (NRSA) , National Cancer Institute
2006	Board Certified in Internal Medicine, Memorial Sloan Kettering Cancer Center
1996	Medical Scientists Training Program (MSTP, Tri-Institutional MSTP program, Weill Cornell Medical College/The Rockefeller University/Memorial Sloan Kettering Cancer Center
1996	Magna cum laude, Mount Holyoke College

Contributions to Science

1. My MD/PhD training in molecular and cellular neuroscience was conducted under the mentorship of Drs. Paul Greengard (The Rockefeller University) and Timothy A. Ryan (Weill Cornell Medical College). I investigated the role of synapsins, a family of highly conserved proteins associated with synaptic vesicles, in the regulation of synaptic transmission and neurotransmitter release. Combining real-time laser scanning microscopy of living hippocampus nerve terminals, molecular biology, and genetically engineered mouse models, I characterized the real-time dynamic association of synapsins with synaptic vesicles during synaptic activities and discovered the activity-dependent regulation of synaptic transmission efficiency by synapsin I through two distinct phosphorylation pathways (e.g., CaMK and MAPK). These studies revealed that multiple signaling pathways act in concert to fine-tune synaptic output in a context-dependent manner.

2. Lineage-specific transcription factor dysregulation in cancer. After residency, I focused my research on chromatin biology and epigenetics, specifically their involvement in transcriptional dysregulation in cancer development. During my postdoctoral training under the tutelage of Dr. C. David Allis at the Rockefeller University and now in my independent laboratory, we discovered that ETV1, an ETS family transcription factor, is a lineage-specific master regulator of GIST and its precursor ICCs (interstitial cells of Cajal) and demonstrated that ETV1 and mutant KIT cooperate in driving GIST oncogenesis. Part of the cooperation is through a positive feedback loop where the ETV1 protein is stabilized by active KIT and downstream MAP kinase signaling; stabilized ETV1 in turn positively regulates KIT expression. We identified a novel synergistic combination therapeutic strategy to target ETV1 protein stability which led to a phase Ib/II clinical trial in patients with GIST (NCT01991379). Further, we uncovered that FOXF1 as an apex master regulator in the core regulatory circuitry (FOXF1, ETV1 and KIT) and established the hierarchy in ICC/GIST lineage specification and pathogenesis. Beyond oncogenic ETV1 and FOXF1 in GIST, we are also interested in understanding oncogenic ETS family transcription factors in different cancer types, and other oncogenic master regulators in cancer. We focus on dissecting the shared and distinct oncogenic effects of aberrantly expressed ETS in different cellular context, mechanisms of their regulation and potential cooperating transcription factor networks in distinct and relevant cancer context. Through mechanistic studies, we are interested in dissecting cancer type/cell lineage-dependent oncogenic behavior and therapeutic sensitivities with the goal to inform therapeutic strategies.

3. Polycomb repressive complex 2 (PRC2) mutation-mediated pathogenesis and therapeutic vulnerability in cancer. Through comprehensive oncogenomic studies, we identified biallelic loss of function mutations in the core components of PRC2 (e.g., EED or SUZ12), concurrent with biallelic genetic inactivation of NF1 and CDKN2A in the majority of human malignant peripheral nerve sheath tumor (MPNST). This has led to the development of H3K27me3 IHC as a clinical diagnostic biomarker for PRC2 loss in cancer and for confirmation of MPNST due to its high prevalence (>80%) in high-grade MPNST. We have uncovered that PRC2 loss in tumor cells drives a context-dependent immune-desert tumor microenvironment (TME) through reprogramming of the chromatin landscape in MPNST and other cancer types. Using functional genomic screens, we have identified that PRC2 loss sensitizes tumor cells to DNMT1 targeted therapy through enhanced viral mimicry and consequent PKR activation, which has led to a phase II study of an oral DNMT inhibitor (ASTX727) in PRC2-loss MPNST. We have further identified that tumor intrinsic PRC2 loss sensitizes them to immunogenic viruses (e.g., Modified Vaccinia Ankara [MVA] and newer generations of engineered MVAs), which are currently under clinical development. We have continued our effort to understand the molecular mechanisms by which tumor intrinsic PRC2 loss impact on chromatin and cellular function and their influences the tumor microenvironment and identify novel therapeutic strategies for cancer with PRC2 inactivation.

4. Genetic and epigenetic mechanisms of oncogene activation and transcriptional dysregulation in cancer. With a group of collaborators, we discovered activating mutations of GPCR-CYSLTR2 in uveal melanoma. We have uncovered a novel mechanism of ALK activation through alternative transcription initiation (ATI) that generates a novel oncogenic ALK isoform (ALKATI) in melanoma and other cancer types. The ALKATI is bi-allelically expressed, epigenetically activated from ERV LTR, independent of genetic alterations at the ALK locus. We are also actively engaged in mechanistic studies of chromatin regulators (e.g., chromatin modifiers, cohesin complex members) and their functional impact of chromatin topology and consequent transcriptional dysregulation in cancer pathogenesis.

5. Clinical translation. As an academic practicing medical oncologist, I am actively involved in designing and conducting early phase clinical investigations based on our laboratory discoveries. I am also actively involved in late phase registration trials in diseases where I have extensive clinical expertise, e.g., GIST and MPNSTs amongst other sarcomas. I have led multiple phase I and phase III trials at MSK and significantly contributed to the FDA-approval of ripretinib in the fourth line treatment of advanced GIST and avapritinib in the first line treatment of PDGFRA exon 18-mutant GIST, including PDGFRA D842V. Our preclinical studies in GIST pathogenesis and therapeutics have led to the success of a phase Ib/II clinical trial (NCT01991379) of combined targeting of KIT and ETV1 protein stability by imatinib plus binimetinib in treatment-naïve GIST (phase II) and in SDH-deficient GIST (phase Ib). These studies have paved the path to a randomized trial comparing imatinib plus a MEK inhibitor vs. imatinib alone in the first-line treatment of advanced GIST (currently in planning). Further, our preclinical studies of MPNST have provided the scientific rationale for a phase II study of the DNMT inhibitor (ASTX727) in MPNST with PRC2 loss (NCT04872543). We will continue our effort to translate laboratory discoveries into clinical investigation in cancer, particularly sarcomas.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

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