RESEARCH BEING DONE USING GCRF FUNDS

The overarching goals are to understand GIST development and pathogenesis. We aim to build models that accurately represent how GISTs behave in the body, and develop new drugs with the potential to cure the disease. The lab is currently exploring the roles of two crucial proteins, FOXF1 and ETV1, that are vital for the survival of certain cancer cells in GISTs, and its research encompasses several innovative projects aimed at improving treatment outcomes. One of the Chi Lab's primary focuses is targeting ETV1 using a combination of two drugs: a KIT inhibitor and a MEK inhibitor (MEKi). This approach is currently being tested in a clinical trial for patients with advanced GIST. Additionally, the lab is investigating whether combining a MEKi with imatinib, the standard treatment for metastatic GISTs, can enhance outcomes as a first-line therapy. This study, conducted as a randomized phase 2 multicenter clinical trial, could hold the potential to revolutionize global care for these patients. The lab is also working on developing new drugs that can target FOXF1, which regulates both KIT and ETV1 genes, making it a favorable target for improving GIST survival rates. Understanding the GIST ecosystem — how the body's normal cells, molecules, and blood vessels contribute to the cancer's survival, metastasis, and drug resistance — is another critical area of research. By gaining insights into these factors, the Chi Lab hopes to create new treatments and develop a comprehensive model of GISTs, particularly focusing on how the cancer spreads to the liver.

PROGRESS REPORT

Clinical Trial: Over the past several years, with the support of GCAF, we have initiated the phase Ib/II clinical trial of imatinib in combination with MEK162 (binimetinib) in advanced GIST (IRB#13-162, NCT01991379) since late 2013. We have completed the phase Ib portion of the study and had demonstrated the safety and defined the recommended phase II doses of the combination therapy in GIST patients. The phase Ib portion of the trial enrolled nine patients in the dose-escalation cohort and 14 in the dose-expansion cohort including six with SDH-deficient GISTs. Imatinib 400 mg daily with binimetinib 45 mg twice daily was established as the RP2D. Dose-limiting toxicity (DLT) was asymptomatic grade 4 creatinine phosphokinase (CPK) elevation. The most common non-DLT grade 3/4 toxicity was asymptomatic CPK elevation (69.6%). Other common ≥grade 2 toxicities included peripheral edema (17.4%), acneiform rash (21.7%), anemia (30.4%), hypophosphatemia (39.1%), and aspartate aminotransferase (AST) increase (17.4%). Two serious adverse events occurred (grade 2 dropped head syndrome and grade 3 central retinal vein occlusion). No unexpected toxicities were observed. Limited clinical activity was observed in KIT-mutant GIST. For SDH-deficient GISTs, one of five had confirmed RECIST1.1 partial response (PR). The median progression-free survival (mPFS) in patients with SDH-deficient GIST was 45.1 months [95% confidence interval (CI), 15.8-not estimable (NE)]; the median overall survival (mOS) was not reached (95% CI, 31.6 months-NE). One patient with a refractory metastatic SDH-deficient GIST had an exceptional pathologic response and durable clinical benefit [1]. Overall, the combination of imatinib and binimetinib is safe with manageable toxicity and has encouraging activity in SDH-deficient but not imatinib-refractory KIT/PDGFRA-mutant GISTs. The observed clinical benefits provide a motivation for a larger trial of the combination strategy in SDH-deficient GISTs. This is recently published [1] and we will seek to incorporate the combination in NCCN guidelines for patients with SDH-deficient GIST.

Dual targeting of the gastrointestinal stromal tumor (GIST) lineage-specific master regulators, ETV1 and KIT, by MEK and KIT inhibitors were synergistic preclinically and may enhance clinical efficacy. The phase II portion of the trial was designed to test the efficacy and safety of imatinib plus binimetinib in first-line treatment of GIST. In this phase II trial (NCT01991379), treatment-naive adult patients with confirmed advanced GISTs received imatinib (400 mg once daily) plus binimetinib (30 mg twice daily), 28-day cycles. The primary end point was RECIST1.1 best objective response rate (ORR; complete response plus partial response [PR]). The study was designed to detect a 20% improvement in the ORR over imatinib alone (unacceptable rate of 45%; acceptable rate of 65%), using an exact binomial test, one-sided type I error of 0.08 and type II error of 0.1, and a planned sample size of 44 patients. Confirmed PR or complete response in > 24 patients are considered positive. Secondary end points included Choi and European Organization for Research and Treatment of Cancer Response Rate, progression-free survival (PFS), overall survival (OS), pathologic responses, and toxicity. Between September 15, 2014, and November 15, 2020, 29 of 42 evaluable patients with advanced GIST had confirmed RECIST1.1 PR. The best ORR was 69.0% (two-sided 95% CI, 52.9 to 82.4). Thirty-nine of 41 (95.1%) had Choi PR approximately 8 weeks. Median PFS was 29.9 months (95% CI, 24.2 to not estimable); median OS

was not reached (95% CI, 50.4 to not estimable). Five of eight patients with locally advanced disease underwent surgery after treatment and achieved significant pathologic response (≥ 90% treatment effect). There were no unexpected toxicities. Grade 3 and 4 toxicity included asymptomatic creatinine phosphokinase elevation (79.1%), hypophosphatemia (14.0%), neutrophil decrease (9.3%), maculopapular rash (7.0%), and anemia (7.0%). The study met the primary end point. The combination of imatinib and binimetinib is effective with manageable toxicity and warrants further evaluation in direct comparison with imatinib in frontline treatment of GIST. This is recently published in JCO [2] and we will seek to incorporate the combination in NCCN guidelines for patients with newly diagnosed GIST.

These trial observations provide the first “proof-of-principle” of the efficacy of targeting the lineage-dependency in GIST. We are actively designing a randomized trial comparing the combination of imatinib plus a MEK inhibitor vs. imatinib in front line setting through the Alliance for Clinical Trials in Oncology.

To date, we have secured commitment from Verastem Oncology to supply their Avutometinib (RAF/MEK inhibitor) and Defactinib (FAK inhibitor) to move forward with an Alliance phase Ib and randomized phase II trial of MEK/FAKi in combination with imatinib in front line treatment of advanced GIST. The trial is currently going through regulatory review at the various committees at the NCI/CTEP/Alliance Oncology group.

Building models for GIST with high risk molecular features (e.g., MAX/MGA mutations) and therapeutic-resistant GIST: Over the past couple of years, we have been consistently developing patient-derived xenografts of all therapeutic-resistant GIST and have developed >10 different PDX models that are resistant to TKIs, including imatinib, sunitinib, regorafenib and ripretinib. We have validated these PDXes and they are ready for further mechanistic and therapeutic investigations.

Further we have developed GIST liver metastasis model using engineered GIST T1 cells with *MAX* deficiency. This model authentically recapitulates the human GIST with increased risk of liver metastasis. We are currently in the process of identifying key factors that contributes to the metastatic behavior because of *MAX* loss. These studies will provide guidance on adjuvant therapy decision. Importantly, they will also provide insights on therapeutic strategies for management of GIST metastasis.

Collection of cfDNA samples for MSK-ACCESS: Over the past couple of years, we, together with Dr. Ciara Kelly, have collected serial blood samples of patients receiving different therapeutic interventions, including patients on the imatinib+binimetinib trial, imatinib, sunitinib, regorafenib or ripretinib single therapy. These samples are being analyzed to evaluate for genetic mechanisms of therapeutic resistance with the goal to develop strategies to overcome the resistance mechanisms.

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.

References:

1. Chi, P., et al., *Phase Ib Trial of the Combination of Imatinib and Binimetinib in Patients with Advanced Gastrointestinal Stromal Tumors.* Clin Cancer Res, 2022. **28**(8): p. 1507-1517.
2. Chi, P., et al., *Phase II Trial of Imatinib Plus Binimetinib in Patients With Treatment-Naive Advanced Gastrointestinal Stromal Tumor.* J Clin Oncol, 2022. **40**(9): p. 997-1008.

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Ping Chi

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

POSITION TITLE: Member and Attending Physician

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
Mount Holyoke College, South Hadley, MA	BA	06/1996	Biochemistry
The Rockefeller University, New York, NY (part of Tri-institutional MSTP program)	PhD	11/2001	Molecular &Cellular Neuroscience
Weill Medical College of Cornell University, New York, NY (part of Tri-institutional MSTP program)	MD	06/2003	Medicine
Brigham and Women's Hospital, Harvard Medical School, Boston, MA	Intern and Resident	06/2005	Resident, Internal Medicine
Memorial Sloan Kettering Cancer Center, New York, NY	Clinical Fellow	08/2011	Hematology/Oncology
The Rockefeller University, New York, NY (concurrent with clinical fellowship)	Postdoc Fellow	08/2011	Chromatin Biology & Epigenetics

A. Personal Statement

I am a NIH-funded physician-scientist who treats patients with sarcoma and melanoma 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 melanoma and 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), melanomas and other cancers.

Ongoing and recently completed projects I would like to highlight include:

5R01CA228216-04 (NIH/NCI)

Chi (PI)

04/01/2018–03/31/2024 (NCE)

Epigenetic mechanisms of transcriptional activation of a novel oncogenic *ALK* variant in cancer

1U01CA252048-01A1 (NIH/NCI)

Chi (PI)

04/01/2021–03/31/2026

Understanding and targeting MAPK pathway activation in NF1-deficient malignant peripheral nerve sheath tumor (MPNST)

R01CA280657 (NIH/NCI)

Chi (PI)

03/01/2023-02/28/2028

Harnessing double stranded-RNA (dsRNA)-response and anti-tumor effect in PRC2-inactivated cancer

W81XWH-22-1-0326 (DOD)

Chi (PI)

05/15/2022-05/14/2025

Reprogram cancer cell and cancer microenvironment for antitumor immunity in NF1-assocaited MPNST

R01FD007544 (OPD/FDA)

Chi (PI)

09/01/2022-08/31/2026

Phase II study of ASTX727 in patients with PRC2 loss MPNST

5P50CA217694-04 (NIH/NCI)

Singer (PI) Antonescu (Project Leader), Role: Basic Science Co-Leader, RP-1

09/01/2018–08/31/2023

MSK SPORE in Soft Tissue Sarcoma, Project 1: Novel therapeutics development and mechanisms of therapeutic resistance in gastrointestinal stromal tumor (GIST)

R01CA265026 (NIH/NCI)

Chen (PI), Role: Co-Investigator

08/01/2022–07/31/2027

Understanding the role of an aberrant hepatic nuclear transcription circuit in prostate cancer tumorigenesis and castration resistance

5R01CA050706-30 (NIH/NCI)

Fagin (PI), Role: Co-Investigator

08/01/2016–11/30/2023

Molecular Pathophysiology of Thyroid Cell Growth

5T32CA009512-33 (NIH/NCI)

Chi (PI)

07/10/2017–06/30/2023 (NCE)

Clinical Scholars Biomedical Research Training Program

GC241229 (Geoffrey Beene Cancer Research Center)

Chi (PI)

09/10/2021–08/31/2023

Understanding MYC-mediated tumorigenesis and plasticity in angiosarcoma

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023-present Attending Physician, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases, New York, NY

2023–Present Member with tenure, Human Oncology and Pathogenesis Program (HOPP), Memorial Sloan Kettering Cancer Center (MSK), New York, NY

2023 Ad hoc member, NIH MCTA study section

2022 NIH Director's New Innovator (DP2) Phase I reviewer

2021, 2022 Ad hoc member, NIH K99 Special Emphasis Panel

2018–Present Associate Professor of Medicine, Weill Cornell Medical College, New York, NY

2018–Present Associate Attending Physician, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases, New York, NY

2018–Present Associate Member, Human Oncology and Pathogenesis Program (HOPP), Memorial Sloan Kettering Cancer Center (MSK), New York, NY

2017 Elected to membership of American Society of Clinical Investigation (ASCI)

2016–2017 Co-chairperson, American Association of Cancer Research (AACR) Special Conference on Advances in Sarcomas: From Basic Science to Clinical Translation, 2017

2015–2021 Chartered Member, American Society of Clinical Oncology (ASCO) Committee: Conquer Cancer Foundation of ASCO Grants Selection Committee

2015–2021 Chartered Member, NIH Peer Review Committee, Clinical Oncology Study Section (CONC)

2015 Ad hoc member, NIH CONC

2012–Present Member, Connective Tissue Oncology Society (CTOS)

2012–2018 Assistant Professor of Medicine, Weill Cornell Medical College, New York, NY

2011–2018 Assistant Attending Physician, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases, New York, NY

2011–2018 Assistant Member, HOPP, MSK, New York, NY

2006–Present Member, AACR

2006–Present Member, ASCO

Honors

2022 DOD NFRP Investigator-Initiated Research Award
2017 Francis S. Collins Scholar, Neurofibromatosis Therapeutic Acceleration Program (NTAP)
2017 Boyer Award in Clinical Research, MSK
2017 Elected to the membership of American Society for Clinical Investigation (ASCI)
2015 DOD NFRP New Investigator Award
2014 The ASCI Young Physician-Scientist Award

2012 Sidney Kimmel Scholar Award

2012 NIH Director's New Innovator Award (DP2)

2011 Clinical Scientist Development Award (K08), National Cancer Institute

2010 Center for Clinical and Translational Science Pilot Project Award, The Rockefeller University

2008 Young Investigator Award (YIA), American Society of Clinical Oncology (ASCO)

2007 F32 Ruth L. Kirschstein National Research Service Awards (NRSA, National Cancer Institute

1996 Elected to Sigma Xi

1996 Elected to Phi Beta Kappa

1996 Magna cum laude, Department of Biochemistry, Mount Holyoke College

1996 American Chemical Society Student Award, the Connecticut Valley Section

1996 Howard Hughes Pre-doctoral Fellowship in Biological Sciences, relinquished because of concurrent MSTP award

1996 Medical Scientists Training Program (MSTP), GM07739, Tri-institutional MSTP program, Cornell University Medical College/The Rockefeller University/Memorial Sloan Kettering Cancer Center

C. Contributions to Science

1. My MD/PhD graduate studies focused on molecular and cellular neuroscience under the guidance of Drs. Paul Greengard (The Rockefeller University) and Timothy A. Ryan (Weill Cornell Medical College), where 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 (i.e., CaMK and MAPK). These studies suggest that the dynamic regulation of synaptic transmission by synapsins is complex and that multiple signaling pathways are employed to fine-tune the regulation in response to distinct context.

a. **Chi P**, Greengard P, Ryan TA. Synapsin dispersion and reclustering during synaptic activity. *Nat Neurosci.* 2001;4(12):1187–1193. PMID: 11685225
b. Feng J, **Chi P**, Blanpied TA, Xu Y, Magarinos AM, Ferreira A, Takahashi RH, Kao HT, McEwen BS, Ryan TA, Augustine GJ, Greengard P. Regulation of neurotransmitter release by synapsin III. *J Neurosci***.** 2002;22(11):4372–4380. PMCID: PMC6758821
c. Yan Z, **Chi P**, Bibb JA [2 authors]. Roscovitine: a novel regulator of P/Q-type calcium channels and transmitter release in central neurons. *J Physiol.* 2002;540(Pt 3):761–770. PMCID: PMC2290289
d. **Chi P**, Greengard P, Ryan TA. Synaptic vesicle mobilization is regulated by distinct synapsin I phosphorylation pathways at different frequencies. *Neuron.* 2003;38(1):69–78. PMID: 12691665

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.

a. **Chi P***, Chen Y*, [10 authors], Sawyers CL. ETV1 is a lineage survival factor that cooperates with KIT in gastrointestinal stromal tumours. *Nature.* 2010;467(7317):849–853. PMCID: PMC2955195 *****Co-first authors. Featured in "News and Views".
b. Chen Y*, **Chi P***, [10 authors], Sawyers CL. ETS factors reprogram the androgen receptor cistrome and prime prostate tumorigenesis in response to PTEN loss. *Nat Med.* 2013;19(8):1023–1029. PMCID: PMC3737318 *Co-first author.
c. Ran L, [16 authors], Chen Y*, **Chi P***. Combined inhibition of MAP kinase and KIT signaling synergistically destabilizes ETV1 and suppress GIST tumour growth. *Cancer Discov.* 2015;5(3):304–315. PMCID: PMC4355391 *****Co-corresponding authors. Featured in "In the Spotlight".
d. Ran L, [18 authors], Chen Y*, **Chi P***. FOXF1 defines the core regulatory circuitry in gastrointestinal stromal tumor (GIST). *Cancer Discov.* 2018; 8(2):234–251. PMCID: PMC5809271 *****Co-corresponding authors. Featured in "In the Spotlight".

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.

a. Lee W, [19 authors], **Chi P***. PRC2 is recurrently inactivated through EED or SUZ12 loss in malignant peripheral nerve sheath tumors. *Nat Genet.* 2014;46(11):1227–1232. PMCID: PMC4249650 *****Corresponding author.
b. Prieto-Granada CN, [3 authors], **Chi P**, Antonescu CR. Loss of H3K27me3 expression is a highly sensitive marker for sporadic and radiation-induced MPNST. *Am J Surg Pathol*. 2016;40(4):479-89. PMCID: PMC4882106.
c. Patel AJ, [24 authors], Chen Y*, **Chi P***. PRC2 inactivating mutations in cancer enhance cytotoxic response to DNMT1 targeted therapy via enhanced viral mimicry. *Cancer Discov*. 2022 Jul 5:cd.21.1671. doi: 10.1158/2159-8290.CD-21-1671. PMID: 35789380. *Co-corresponding authors.
d. Yan J, [23 authors], Chen Y*, **Chi P***. Tumor-intrinsic PRC2 inactivation drives a context-dependent immune-desert microenvironment and is sensitized by immunogenic therapeutic viruses. *J Clin Invest*. 2022; Jul 19:e153437. doi: 10.1172/JCI153437. PMID: 35852856. *Co-corresponding authors.

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 (*ALK*^{ATI}) in melanoma and other cancer types. The *ALK*^{ATI} 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.

a. Wiesner T, [28 authors], Chen Y*, **Chi P***. Alternative transcription initiation leads to expression of a novel *ALK* isoform in cancer. *Nature.* 2015;526(7573):453–457. PMCID: PMC4807020 *****Co-corresponding authors.

b. Moore AR, [10 authors], **Chi P**, Sakmar TP, Chen Y. Recurrent activating mutations of G-protein-coupled receptor CYSLTR2 in uveal melanoma. *Nature Genet.* 2016;48(6):675–680. PMCID: PMC5032652.

c. Shukla S, [21 authors], **Chi P*,** Chen Y*. Aberrant activation of a gastrointestinal transcriptional circuit in prostate cancer mediates castration resistance. *Cancer Cell*. 2017;32(6):792–806. PMCID: PMC5728174 *****Co-corresponding authors.

d. Tang F, [26 authors], **Chi P**, [3 authors], Khurana E. Chromatin profiles classify castration-resistant prostate cancers suggesting therapeutic targets. *Science*. 2022; 376(6596):eabe1505. PMCID: PMC9299269.

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.

a. Blay JY, [9 authors], **Chi P**, [5 authors], von Mehren M. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled,

phase 3 trial. Lancet Oncol. 2020;21(7):923-934. PMCID: PMC8383051.

b. **Chi P***, [26 authors], Tap WD. Phase II trial of imatinib plus binimetinib in patients with treatment-naive advanced gastrointestinal stromal tumor. *J Clin Oncol.* 2022;40(9):997-1008. PMCID: PMC8937014. *Corresponding author.

c. **Chi P***, [22 authors], Tap WD*. Phase Ib trial of the combination of imatinib and binimetinib in patients with advanced gastrointestinal stromal tumors. *Clin Cancer Res.* 2022;28(8):1507-1517. PMCID: PMC9012681. *Co-corresponding authors.

d. Antonescu CR, Reuter VE, Keohan ML, Hwang S, **Chi P**. DICER1-associated anaplastic sarcoma of the kidney with coexisting activating PDGFRA D842V mutations and response to targeted kinase inhibitors in one patient. *JCO Precis Oncol*. 2022 Jul;6:e2100554. doi: 10.1200/PO.21.00554. PMID: 35797510.

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