# Understanding the molecular determinants of GIST pathogenesis and novel therapeutics development in GIST

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## *Scientific Abstract:*

Gastrointestinal stromal tumor (GIST) is a rare type of cancer that affects approximately 40,000 patients with an annual incidence of 5,000 cases in the US. It arises from the “pacemaker” cells of the gastrointestinal tract and is mainly characterized by activating mutations in *KIT* or *PDGFRA* receptor tyrosine kinases. Despite the initial clinical success of imatinib that targets mutant *KIT/PDGFRA*, nearly all advanced GIST patients develop imatinib-resistance and eventually die of their disease. It is critical to gain a better understanding of the pathogenesis of GIST to dissect the molecular underpinning of aggressive and metastatic behaviors and to develop novel treatment strategies that enhance first-line imatinib therapy and target and/or prevent imatinib-resistance.

Previous studies have focused on understanding and targeting the ICC/GIST lineage-specific transcriptional factor, *ETV1*, in preclinical models and in an investigator initiated “phase Ib/II study of binimetinib in combination with imatinib in patients with untreated advanced GIST” to directly evaluate the safety and clinical efficacy of this novel combination therapy in advanced GIST. The phase Ib portion of the study has been completed and has demonstrated the safety and defined the recommended phase II doses of the combination therapy in GIST patients. In a small expansion cohort of patients with SDH-deficient GIST, the combination therapy has shown promising efficacy (Chi P et al., CCR 2022). The phase II study has completed accrual and met the primary endpoint with best RECIST objective response rate (ORR) of 68.3% (two-sided 95% CI, 51.9-81.9%; one-sided 90% CI, 57.2-100%) (Chi P, et al., JCO 2022). The current proposal focuses on a new set of aims: 1) evaluate therapeutic resistance mechanisms to ripretinib (a newly FDA approved 4$^{th}$ line therapy) by MSK-IMPACT and MSK-ACCESS (liquid biopsy), 2) evaluate the efficacy and resistance to a new generation of receptor tyrosine kinase inhibitor (TKI), NB003, that potently targets a spectrum of secondary resistant mutations in KIT and PDGFRA, but does not cross react with VEGFR, in a first in human phase I trial, where I am the global PI, and 3) discover, validate, and incorporate molecular determinants of aggressive and metastatic clinical behavior in GIST preclinical models and inform adjuvant imatinib therapeutic decisions in GIST management (in collaboration with Dr. Cristina Antonescu). These studies, if successful, has the potential to change the landscape of clinical practice in GIST management.

## *Lay Abstract:*

Gastrointestinal stromal tumor (GIST) is a rare type of cancer that arises from the “pacemaker” cells of the gastrointestinal tract and is mainly characterized by activating mutations in *KIT* or *PDGFRA* receptor tyrosine kinases. There is a critical need for novel and more effective drug treatment for patients with advanced GISTs, and ETV1 has been recently established as a critical survival factor and a novel drug target in GIST. Here, we propose to evaluate the resistance mechanisms to newer generation of TKIs, including the recent FDA approved 4$^{th}$ line therapy, ripretinib and a newer TKI in clinical development, NB003 and to discover and investigate the molecular determinant involved in GIST metastatic behavior and inform adjuvant therapeutic decisions in GIST.

## *Project Narrative:*

## *A. TITLE:* Understanding the molecular determinants of GIST pathogenesis and novel therapeutics development in GIST

## *B. INTRODUCTORY STATEMENT, BACKGROUND AND RATIONALE:*

*B1. Molecular characteristics of gastrointestinal stromal tumor (GIST):* GIST represents one of the most common subtypes of human sarcomas. It arises in the interstitial cells of Cajal (ICCs), the pacemaker cells located throughout the muscle wall of the entire GI tract. Similar to its precursor ICCs, GIST expresses high levels of KIT receptor tyrosine kinase (RTK) [1, 2]. The majority of GISTs harbor activating mutations in *KIT* and *PDGFRA* [2-4]. A small subset harbor mutations in *BRAF, RAS,* or *NF1* that aberrantly activate the MAP kinase (MAPK) pathway [5-7]. About 15% of tumors lack mutations in *KIT/PDGFRA* and are designated as wild-type (WT) GISTs. Most WT GISTs harbor genetic or epigenetic alterations that specifically inactivate the SDH pathway. These mutations are thought to function as oncogenic "drivers" required for growth and survival of GISTs. These observations have provided the scientific rationale for clinically targeting these mutations.

*B2. Current standard of care of advanced GIST:* A diagnosis of GIST has similar natural behavior and response patterns, and carries a 5 year survival of ~45% [8-11]. Imatinib (Gleevec®), a multi-targeted tyrosine kinase inhibitor (TKI) that targets KIT/PDGFRA, is the standard first line therapy in advanced GIST. It has a response rate (RR) of approximately 45-52%, an overall disease control rate of 80% to 85% and a median progression free survival (PFS) of 20 to 24 months [10-13]. Despite early clinical success, the majority of patients with advanced disease develop resistance to imatinib within 2-3 years of treatment [13, 14]. Second and third line therapies have limited efficacy [14-17]. This clearly indicates that a general resistance to this class of inhibitors develops once the disease progresses on imatinib. Despite these observations, progress has been slow in identifying novel therapeutic strategies that: 1) are more effective than first line imatinib therapy, 2) can overcome imatinib-resistance in GIST management, or 3) can prevent the development of resistance to first line therapy.

*B3. Challenges of clinical management of GIST:* Approximately 5-10% of patients with GIST have primary resistance to imatinib. Another 15% of patients develop early resistance within 3 months of treatment. The majority of patients will develop imatinib resistance after approximately 2-3 years of treatment. This general resistance leads to a rapid clinical decline and eventual death [18]. Developing novel therapeutics for imatinib-resistant disease has been challenging. The mechanisms of imatinib resistance in GIST are heterogeneous. Secondary *KIT* mutations are rare in primary resistance, but are found in about 50-67% of patients with acquired resistance [18, 19]. The remaining cases of secondary resistance have unknown etiologies. Recent data suggest that the GIST stem/progenitors are *KIT*-low and *KIT*-independent and therefore imatinib-insensitive [20], accounting for part of the resistance mechanisms in both the primary and secondary settings. In summary, although *KIT* inhibitors have revolutionized the treatment of advanced GIST, their efficacy is not indefinite, nor are they curative [4, 12, 13, 15, 21-23]. Imatinib resistance is the most significant challenge in the current management of advanced GIST. The need is particularly acute for novel therapeutics that can 1) overcome imatinib resistance, 2) delay or prevent the development of resistance to TKIs, especially in the first-line setting.

*B4. ETV1, an ETS family transcription factor, as a novel therapeutic target in GIST:* To search for novel therapeutic target, we have uncovered that *ETV1* is a lineage-specific master transcription factor required for ICC development and GIST oncogenesis [24, 25]. We have established the *in vivo* requirement of *ETV1* in GIST tumor initiation and maintenance. We further demonstrated that the ETV1 protein is stabilized by active MAP kinase signaling downstream of KIT/PDGFRA signaling and that stabilized ETV1 positively regulates *KIT* expression, forming a positive feedback circuit in GIST pathogenesis[24, 25]. We have also demonstrated that ETV1 is required for the survival of both imatinib-sensitive and –resistant GIST cells[24, 25], as well as for the survival of GIST stem/progenitor cells [20] (personal communications, Dr. Tomas Ordog, Mayo Clinic). Further, adaptive response and resistance to targeted therapy has emerged as a clinically important entity for persistent disease and development of therapeutic resistance in melanoma targeted therapy with RAF inhibitors [26-28]. Our preliminary data suggests that ETV1 is involved in the adaptive response and resistance to imatinib treatment in GIST (data not shown). Therefore, targeting ETV1 may not only offer a new way to address the intrinsically imatinib-resistant GIST stem cell/progenitor population, but also delay and/or prevent the

development of imatinib resistance if it is inhibited early in the upfront setting. Targeting ETV1 may offer broad benefit to all GIST patients, including those with *KIT/PDGFRA*-mutant and WT GISTs.

*B5. Combination of MEK inhibition and KIT inhibitor to target ETV1 is synergistic*: Reasoning that the ETV1 protein is stabilized by active MAP kinase signaling downstream of mutant *KIT/PDGFRA*-mediated oncogenesis [24], we first tested a single agent MEK inhibitor that inhibits the MAP kinase pathway to target ETV1 protein stability. We observed that treatment of the GIST cells with a MEK inhibitor or a KIT inhibitor can result in rapid destabilization of the ETV1 protein via the proteosomal-dependent degradation pathway within hours, whereas the ETV1 transcript remains stable [24]. We have also observed that ETV1 protein destabilization correlates well with sensitivity to KIT or MEK inhibitors. However, MEK inhibitor alone does not induce sustained blockade of the MAP kinase pathway and delivers less durable destabilization of the ETV1 protein. This is likely due to feedback reactivation of cell lineage specific RTKs such as KIT or PDGFRA. When we combined the MEK inhibitor with imatinib, the combination therapy induced significantly more durable MAP kinase pathway inhibition and ETV1 protein destabilization, more apoptosis compared to either drug alone. Moreover, while imatinib or MEK162 alone mostly stabilized tumor growth, the combination of imatinib and MEK162 leads to complete responses even at reduced doses of MEK162 in various preclinical GIST models [25]. These data suggest that the combination strategy induces potent cell death and may have the potential to cure patients with advanced GIST.

*B6. Molecular determinants of metastatic and aggressive GIST:* The molecular underpinnings of aggressive behavior, e.g., early metastasis, rapid tumor progression, enhanced cellular plasticity, in GIST remain unclear. Previously identified oncogenic factors, including mutant *KIT/PDGFRA* and expression of master regulators *ETV1/FOXF1* do not predict aggressive clinical behavior. Low expression of *CDKN2A* was associated with aggressive clinical behavior;[38,39] but, its role in tumor progression, sensitivity to imatinib, and OS remain undetermined. Expression of two rarely mutated accessory transcription factors (TFs), *HAND1* and *BARX1*, correlates with metastatic and aggressive small bowel and indolent gastric GIST, respectively, in retrospective studies;[40,41] their prognostic and pathogenic roles remain to be validated. Discovering and understanding the molecular determinants of aggressive clinical behaviors is critical for adjuvant treatment consideration for resected GIST and may inform novel therapeutic strategies for metastatic GIST.

*B7. Scientific premise and overall hypothesis:* Despite the early clinical successes of imatinib and other TKIs in GIST, the clinical benefit is not durable, and patients eventually develop imatinib and other TKI-resistance and succumb to their disease. We have previously focused on targeting lineage dependencies and successfully completed a phase Ib/II clinical trial of combination of imatinib plus binimetinib in GIST (Chi P et al., CCR, 2022; Chi P. et al., JCO 2022). We will continue our endeavor in investigation of therapeutic resistance mechanisms to new generations of TKIs, e.g., ripretinib, NB003 in Aim 1 (new).

Further, our recent pan-cancer genomic characterization of metastatic patterns showed that fraction of genome altered (FGA), tumor mutational burden (TMB), and genetic alterations in cell cycle and MYC pathways were enriched in metastatic vs. primary GIST.[42] Similarly, biallelic loss of function (LOF) mutations in *MAX* or *MGA* (each 5%), and *MYC* amplifications (0.5%), were enriched in untreated metastatic GIST compared to primary localized GIST. Further, tumors with arm-level CNAs, e.g., *-1p* (50%), *-9p* (25%), *+1q*, *+5p*, and *+5q*, or gene alterations in the *MAX/MGA/MYC axis*, *NKX2.1*, and *SDHB* were enriched in untreated metastatic vs. non-metastatic GIST ($p<0.05$), and most were associated with worse RFS ($p<0.001$). MAX belongs to a basic helix-loop-helix leucine zipper (bHLHZ) TF network, is the obligative heterodimerization activator of MYC, and modulates MYC regulation of cell growth, survival, and metabolism. MAX also interacts with MGA, a core component of the PRC1.6 complex that regulates cellular differentiation.[43-48] Prior genomic studies[49,50] identified that *MAX* mutations were associated with GIST progression and imatinib-resistance but lacked mechanistic investigation. *MAX* inactivation had been described as an early event in a subset of low risk and micro-GISTs, which contributes to GIST initiation.[51] Our findings concur that *MAX* alterations are likely an early event, detected at baseline in all except one case (7/8), but *MAX/MGA/MYC* alterations occurred in *high-* rather than low-risk GIST, suggesting a distinct function of *MAX* inactivation in metastasis. *MYC* amplification/overexpression is also implicated in functional inactivation of the MGA complex through interaction with MAX.[52,53] Thus, *MAX/MGA/MYC* alterations in GIST converge to inactivate the MAX/MGA containing PRC1.6 complex, deregulating cellular differentiation and plasticity and consequently promoting tumor progression and metastasis. Our preliminary data indicate that *MAX/MGA/MYC* alterations and arm-level CNAs in GIST may serve as novel molecular biomarkers

associated with aggressive and metastatic behavior in GIST and help guide adjuvant imatinib therapy. Here, we focus on mechanistic (Aim 2) and translational clinical investigations (Aim 3, in collaboration with Dr. Cristina Antonescu).

*We hypothesize that genetic perturbations of MAX/MGA/MYC and arm-level CNAs in GIST promote tumorigenesis and aggressive metastatic behavior and may represent independent molecular risk biomarkers for GIST relapse and facilitate discovery of rational pathway targets for metastatic GIST*. Here, we employ preclinical *in vitro* and *in vivo* GIST models coupled with state-of-the-art epigenomic, transcriptomic, and single cell analyses to investigate the mechanisms by which *MAX/MGA/MYC* perturbation contributes to GIST cellular differentiation and plasticity, tumor progression, and metastasis (Aim 2). We will leverage our unique and comprehensive clinical and molecular NGS data to generate molecular prognostic biomarkers to guide imatinib adjuvant therapy, especially in clinical gray-zones with conflicting clinical benefit data for the 25-40% of intermediate-risk resected GISTs.[29-34] We will specifically investigate large-scale genomic landscape signatures, focusing on selecting and validating prognostic biomarkers of tumor progression, thus generating next-generation risk nomograms. Moreover, we will integrate these molecular biomarkers with conventional pathologic risk metrics to provide a combinatorial risk assessment using machine learning (ML) to guide adjuvant therapy (Aim 3, in collaboration with Dr. Antonescu). This project could change clinical practice in adjuvant treatment of GIST and identify novel therapeutic strategies for metastatic GIST beyond TKIs.

## C. SPECIFIC AIMS:

**Previous Aims**

**Aim 1:** Evaluate the resistance mechanisms to the combination therapy of imatinib+ binimetinib using biopsy samples derived from the phase II portion of the investigator-initiated trial, "A Phase Ib/II study of MEK162 in combination with imatinib mesylate in patients with untreated advanced gastrointestinal stromal tumor (GIST) (IRB #13-162, NCT01991379)". (**completed and published recently- see Progress section**)

**Aim 2:** Evaluate the resistance mechanisms to the recent FDA approved 4$^{th}$ line therapy, ripretinib, in advanced GIST, using MSK-IMPACT and MSK-ACCESS liquid biopsies. **(completed, manuscript in preparation)**

**New Aims:**

**Aim 1:** Evaluate the efficacy and resistance mechanisms of a new generation of TKI, NB003 in preclinical models and first-in-human clinical trial (NCT04936178).

**Aim 2.** Elucidate the molecular mechanisms of *MAX/MGA/MYC* genetic perturbations involved in enhanced cellular plasticity, migration, and metastatic behavior in GIST pathogenesis. We focus on MAX/MGA/MYC and MAX/MGA-PRC1.6 complex interactions with chromatin and their functional impact using engineered *MAX/MGA/MYC*-isogenic human GIST cellular systems and multi-omics. Subaims will characterize the effect of *MAX/MGA/MYC* permutation on **1a**) transcriptome, cistrome, epigenome, and GIST cellular behavior *in vitro*, **1b**) GIST tumorigenesis, metastatic behavior, and tumor microenvironment *in vivo*, **1c**) cellular plasticity, tumor heterogeneity, and tumor evolution using single cell (sc) RNA-seq and scATAC-seq and a novel CellTag system[7] *in vitro* and *in vivo*.

**Aim 3. Identify and validate molecular biomarkers predictive of recurrence risk and adjuvant therapy determination in primary GIST after resection (in collaboration with Dr. Cristina Antonescu)**. We focus on developing a combinatorial risk assessment tool that integrates novel molecular biomarkers (CNAs [e.g., *-1p*], genetic alterations [e.g., *MAX/MGA/MYC*]) and conventional pathologic risk metrics (e.g., tumor size, location, and mitotic account) using ML. The goal is to improve recurrence risk assessment in GIST and facilitate adjuvant therapy decisions. Subaims include **2a)** discover and validate predictive molecular biomarkers for RFS, using a discovery and 2 validation cohorts (pre-imatinib and prospective, **Table 1**), **2b**) establish an optimal conventional predictive model using conventional metrics and competing risk classification and regression tree (CART) decision tree analysis, **2c**) generate a combinatorial pathologic-genomic nomogram using ML approaches to integrate molecular predictor and the optimal conventional risk stratification model.

## D. SIGNIFICANCE AND STATEMENT OF RELEVANCE TO GIST

These studies will change the clinical management landscape for all settings of patients with GIST. The proposed translational and preclinical studies will also facilitate our understanding of GIST aggressive behavior, therapeutic resistance and help inform molecular determinants of GIST recurrence risks and adjuvant therapeutic decisions and facilitate future novel therapeutic development.

## E. RESEARCH BEING DONE USING GCRF FUNDS

As described in section D, all the correlative studies including analysis of protein, pathology specimen, genetics and transcriptomes and MSK-IMPACT, MSK-ACCESS, sample collections will be performed by the Chi laboratory and collaborators. These endeavors will be supported by the GCRF funds.

## F. PROGRESS REPORT

**F1-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 [29]. 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 [29] 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 [30] 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.

**F2-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. These are special resources that can be used in the proposed new aims as well.

**F3- 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 5$^{th}$ 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 6$^{th}$ and 19$^{th}$ 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.

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26. Chapman, P.B., D.B. Solit, and N. Rosen, *Combination of RAF and MEK inhibition for the treatment of BRAF-mutated melanoma: feedback is not encouraged.* Cancer Cell, 2014. **26**(5): p. 603-4.
27. Lito, P., N. Rosen, and D.B. Solit, *Tumor adaptation and resistance to RAF inhibitors.* Nat Med, 2013. **19**(11): p. 1401-9.
28. Solit, D.B. and N. Rosen, *Towards a unified model of RAF inhibitor resistance.* Cancer Discov, 2014. **4**(1): p. 27-30.
29. 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.
30. 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.
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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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