Origins of the NIH Pediatric GIST Clinic
ASCO 2006
the NIH Pediatric & Wildtype GIST Clinic
Established 2008
Outline

• Background data-how targeted Rx directed at KIT/PDGFRα mutations with imatinib changed disease course in GIST
• Pediatric GIST-lack KIT/PDGFRα mutations
• Identification and management principles of SDH-deficient GIST
Gastrointestinal Stromal Tumors: GIST

- Most common mesenchymal neoplasms of the gastrointestinal track; but fewer than 1% all GI tumors

- Originates in the Interstitial Cells of Cajal (smooth muscle pacemakers)

- Introduced as a diagnostic term in 1983

- Initially, management was mostly surgical
- Response to chemotherapy < 5%
- ICC were found to express high levels of cKIT
- GISTs were found to have cKIT and PDGFRA activating mutations
- Imatinib (tyrosine kinase inhibitor first approved for CML, that also inhibits cKIT and PDGFRA) approved for unresectable and metastatic GIST in 2002
- 2 Year survival has increased from 20% to 75-80%
- Well described criteria for use in high risk resected tumors has decreased risk of recurrence

![IMATINIB GREATLY IMPROVED SURVIVAL IN GIST](image)
Frequency of SDHB-negative and SDHB-positive gastric GISTs as a function of age

Miettinen et. al
Am J Surg Pathol.
2011
GIST Molecular Subtypes

- 65% SDH+ Unknown
- 21% PDGFRA
- 9% BRAF
- 4% KIT
- 1% SDH-deficient
- Esophagus <1%
- Stomach 56%
- Small intestine 32%
- Colon/rectum <6%
- Other <6%

References:
- Rossi et al., Am J Pathol 2015
- Søreide et al., Cancer Epidemiology 2016
- Miettinen et al., Am J Surg Pathology
The NIH pediatric and wildtype GIST clinic

- Bi-annual/annual clinic at NIH established June, 2008
  - Collaborative effort between clinicians, researchers, support groups and patients
  - Objective: further the investigation of the clinical features and oncogenic mechanisms underlying wild-type GIST

**Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations.**


**Succinate Dehydrogenase Mutation Underlies Global Epigenomic Divergence in Gastrointestinal Stromal Tumor**

J. Keith Killian1, Su Young Kim1, Markku Miettinen1, Carly Smith1, Maria Marino1, Maria Tsokos1, Martha Quezado1, William I. Smith Jr2, Mona S. Jahromi1, Paraskevi Xekouki1, Eva Szarek1, Robert L. Walker1, Jerzy Lasota4, Mark Raffeld1, Brandy Klotzle1, Zengfeng Wang1, Laura Jones1, Yuelin Zhu1, Yonghong Wang1, Joshua J. Waterfall1, Maureen J. O’Sullivan7, Marina Bibikova4, Karel Pacák1, Constantine Stratakis1, Katherine A. Janeway6, Joshua D. Schiffman4, Jian-Bing Fan2, Lee Helman1, and Paul S. Meltzer1

**Molecular Subtypes of KIT/PDGFR Wild-Type Gastrointestinal Stromal Tumors**

A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic

**Surgical Management of Wild-Type Gastrointestinal Stromal Tumors: A Report From the National Institutes of Health Pediatric and Wildtype GIST Clinic.**

Weldon CB1, Madenci AL1, Boikos SA1, Janeway KA1, George S1, von Mehren M1, Pappo AS1, Schiffman JD1, Wright J1, Trent JC1, Pacak K1, Stratakis CA1, Helman LJ1, La Quaglia MP1.
SDH Deficient GIST

Janeway K, Inherited and Syndromic GIST. In: Gastrointestinal Stromal Tumors: Bench to Bedside (Scoggins CR, Raut CP, Mullen JT eds.) Based on Boikos S., JAMA Oncology 2016
globally hypermethylated and stable genomes

KIT Mutant GIST

SDH Mutant GIST

Killian K et al. Cancer Discovery 2013
Consequences of dSDH

• Increased succinate/\(\alpha\)KG ratios due to dSDH inhibits \(\alpha\)KG dependent dioxygenase catalyzed reactions:
  • TET2 → global DNA hypermethylation
  • PHD → pseudo hypoxic state due to accumulation of HIF-1\(\alpha\) thru blockade of HIF prolyl hydroxylation
  • Histone demethylase JMJD3 → histone methylation
SDH mutations

- We have found mutations in all 4 SDH genes (A,B,C,D)-most of these (80%) are germline
- We have also found silencing of SDHC by “epimutation”-hypermethylation of the SDHC promoter
- Why does this matter? SDH mutations and epimutations lead to both Carney Triad and Carney-Stratakis syndrome -most critical issue is paragangliomas (PG).
- These distinctions are important for genetic counseling and screening for PG
What We Have Learned

- Best screen is SDHB IHC
- dSDH GISTs overwhelmingly gastric in location and most are multifocal and/or metastatic at presentation
  - Implications for management
  - Only 1 small bowel dSDH GIST
- None respond to imatinib; definite responses to sunitinib and regorafenib
  - Likely due to effects on VEGF
- Most SDH mutations are germline
  - Implications for genetic counseling
Surgical Approach

- Potential benefits of surgery must be tempered by the long-term morbidity of extensive resections in a disease that may persist for decades even when there is recurrence or disease is advanced

- 76 patients at the NIH GIST clinic SDH deficient GIST
  - Pathology reviewed at NIH
  - Surgical reports reviewed by 2 surgeons
  - Resection classified R0, R1, R2

- Median EFS 2.5 years
- Overall survival 90%

- Among patients with non-metastatic disease, R0 resection was not significantly associated with improved EFS

- We recommend gastric wedge resection with regional lymph node examination rather than radical approaches like gastrectomy

Weldon, CW et al; JCO 2017
Cancer Risk

• SDH-deficient GIST
  • 80% germline
  • Risk of: paraganglioma / pheochromocytoma / RCC
  • Referral to cancer risk program

• NF-1 associated GIST
Future Directions

- Continue to accrue patients with dSDH GIST
  - Study genotype/phenotype correlations
  - Need cell lines and/or models!
    - Dr. Sicklick at this meeting describing cell lines
    - We are still learning (SmBowel dSDH GIST just discovered)
- Based on increased succinate/$\alpha$KG ratios $\rightarrow$ global DNA hypermethylation + PHD inhibition “pseudo-hypoxic” state
- Test more potent DNMT inhibitors, e.g., SGI-110 (guadecitabine) study opened at NCI
  - Combinations (maybe with anti-angiogenic drugs)
- Understand disease over time
- Develop prognostic marker (cfDNA-hypermethylation)
“At the GIST Clinic at the POB, everybody can share stories with people who are dealing with what you are. An awesome experience and I am learning so much.”

Jennifer and Alyssa, GIST patient