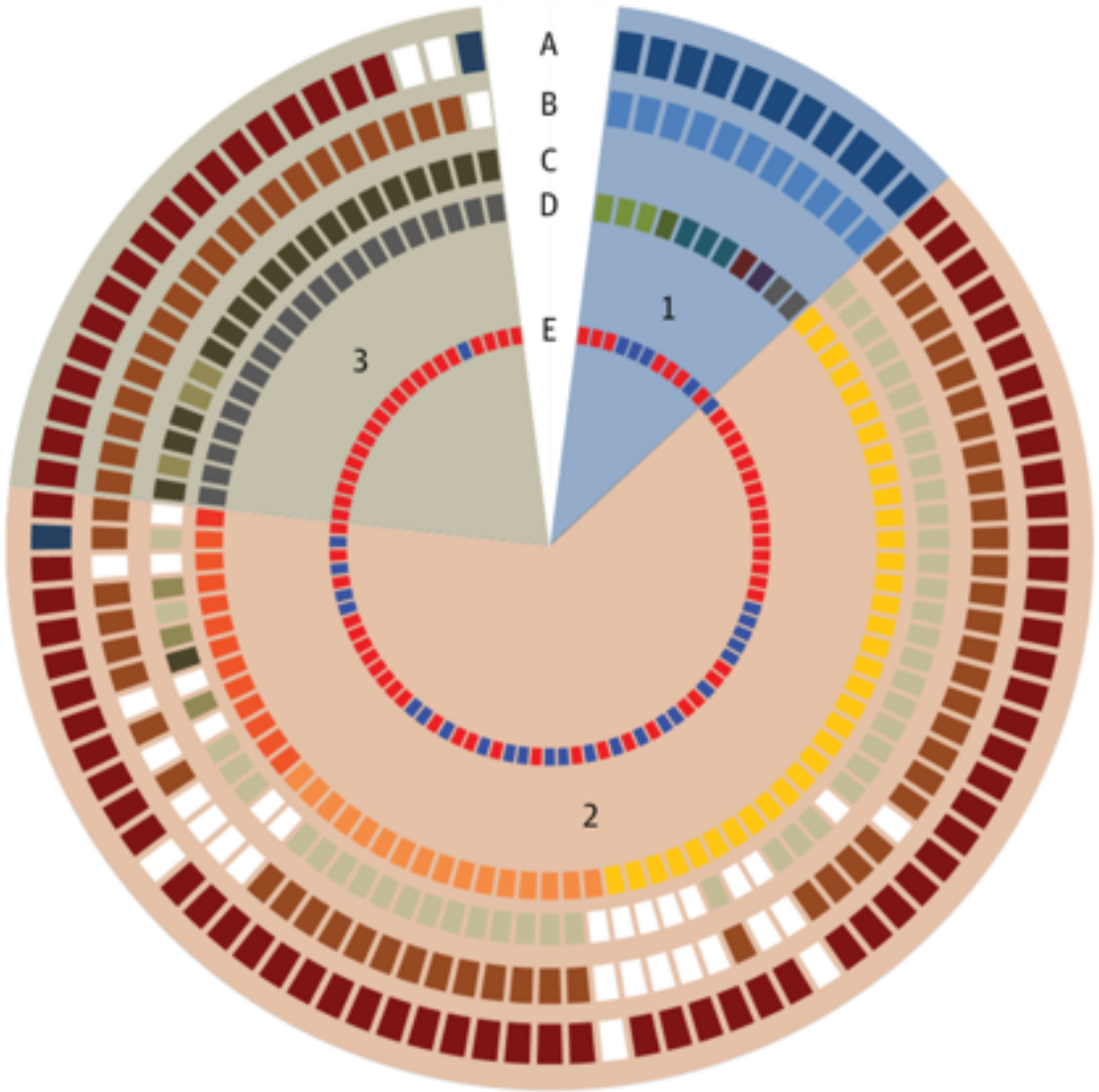
the NIH Pediatric & Wildtype GIST Clinic

Established 2008

Total of 95 GIST Pts Analyzed



Groups
1 Normal SDHB expression
2 *SDHB* mutation
3 *SDHC* promoter methylation[a]

Circles
A. SDHB IHC: Present; Absent
B. Tumor global methylation: Centrist; Deviator
C. Tumor *SDHC* methylation zygosity: Homozygous; Hemimethylated; Not found
D. Mutations[b]: *NF1*; *CBL*; *BRAF*; *ARID1A*; *KIT/PDGFRA* fusion; *SDHA*; *SDHB*; *SDHC*; *SDHD*; None
E. Sex: Male; Female; Missing information

From: **Molecular Subtypes of KIT/PDGFRA Wild-Type Gastrointestinal Stromal Tumors: A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic**

JAMA Oncol. Published online March 24, 2016. doi:10.1001/jamaoncol.2016.0256

Table. Patient Demographics and Tumor Characteristics

Characteristic	Group 1: SDH-Competent GIST (n = 11)	Group 2: SDHX-Mutant GIST (n = 63)	Group 3: SDHC-Epimutant GIST (n = 21)	All Patients (n = 95)
Age, median (range), y[a]	46 (30-78)	23 (7-58)	15 (8-50)	23 (7-78)
Female sex, No. (%)[b]	7 (64)	39 (62)	20 (95)	66 (70)
Tumor size at resection, median (range), cm	8.9 (4.7-13.5)	5.6 (1.5-21)	4.7 (2-16)	5.6 (1.5-21)
Focality, proportion (%)[c,d]				
Unifocal	9/10 (90)	33/55 (60)	5/18 (28)	47/83 (57)
Multifocal	1/10 (10)	22/55 (40)	13/18 (72)	36/83 (43)
Primary location, No. (%)[e]				
Gastric	1 (9)	63 (100)	21 (100)	85 (89)
Small bowel	9 (82)	0	0	9 (9)
Abdominal	1 (9)	0	0	1 (1)
Histologic subtype, proportion (%)[d,f]				
Epithelioid	1/11 (9)	22/59 (37)	9/20 (45)	32/90 (36)
Spindle	9/11 (82)	9/59 (15)	2/20 (10)	20/90 (22)
Mixed	1/11 (9)	28/59 (47)	9/20 (45)	38/90 (42)
Metastasis at presentation, proportion (%)[d]				
Liver	0/10	12/58 (21)	7/19 (37)	19/87 (22)
Peritoneum	1/10 (10)	6/58 (10)	1/19 (5)	8/87 (9)
Lymph nodes	0/4	15/21 (65)	3/8 (38)	18/35 (51)
No liver or peritoneal metastases at presentation, proportion (%)[d]	9/10 (90)	41/58 (71)	13/19 (63)	63/87 (71)

Abbreviations: GIST, gastrointestinal stromal tumor; SDH, succinate dehydrogenase.

[a] There was a significant difference in age between the 3 groups ($P < .001$). Pairwise comparisons were significantly different: group 1 vs 2, $P < .001$; group 1 vs 3, $P < .001$; group 2 vs 3, $P = .002$.

[b] There was a significant difference in distribution of sex by group ($P = .03$), in pairwise comparisons, there was no difference between groups 1 and 2 ($P = .91$), but the distribution of sex differed significantly between group 1 and group 3 ($P = .02$) and between group 2 and group 3 ($P = .004$).

[c] There was a significant difference between focality of presentation for SDH-competent and SDH-deficient GIST ($P = .02$).

[d] The number of cases is less than the number of patients because of incomplete information.

[e] There was a significant difference in the distribution of primary location of tumors. All group 2 and 3 patients had gastric tumors while 1 of 11 group 1 patients had a gastric tumor ($P < .001$).

[f] There was a significant difference in histologic subtype among the groups. Group 1 vs 2: $P = .001$; group 1 vs 3: $P < .001$; group 2 vs 3: $P = .76$.

Table Title:

Patient Demographics and Tumor Characteristics

What We Have Learned

- **Best screen is SDHB IHC**
- **dSDH GISTs overwhelmingly gastric in location and most are multifocal and/or metastatic at presentation (just identified 1st small bowel dSDH GIST)**
  - Implications for management
  - Just identified our first small bowel dSDH GIST
- **None respond to imatinib; definite responses to sunitinib and regorafanib**
  - Likely due to effects on VEGF
- **Most SDH mutations are germline**
  - Implications for genetic counseling

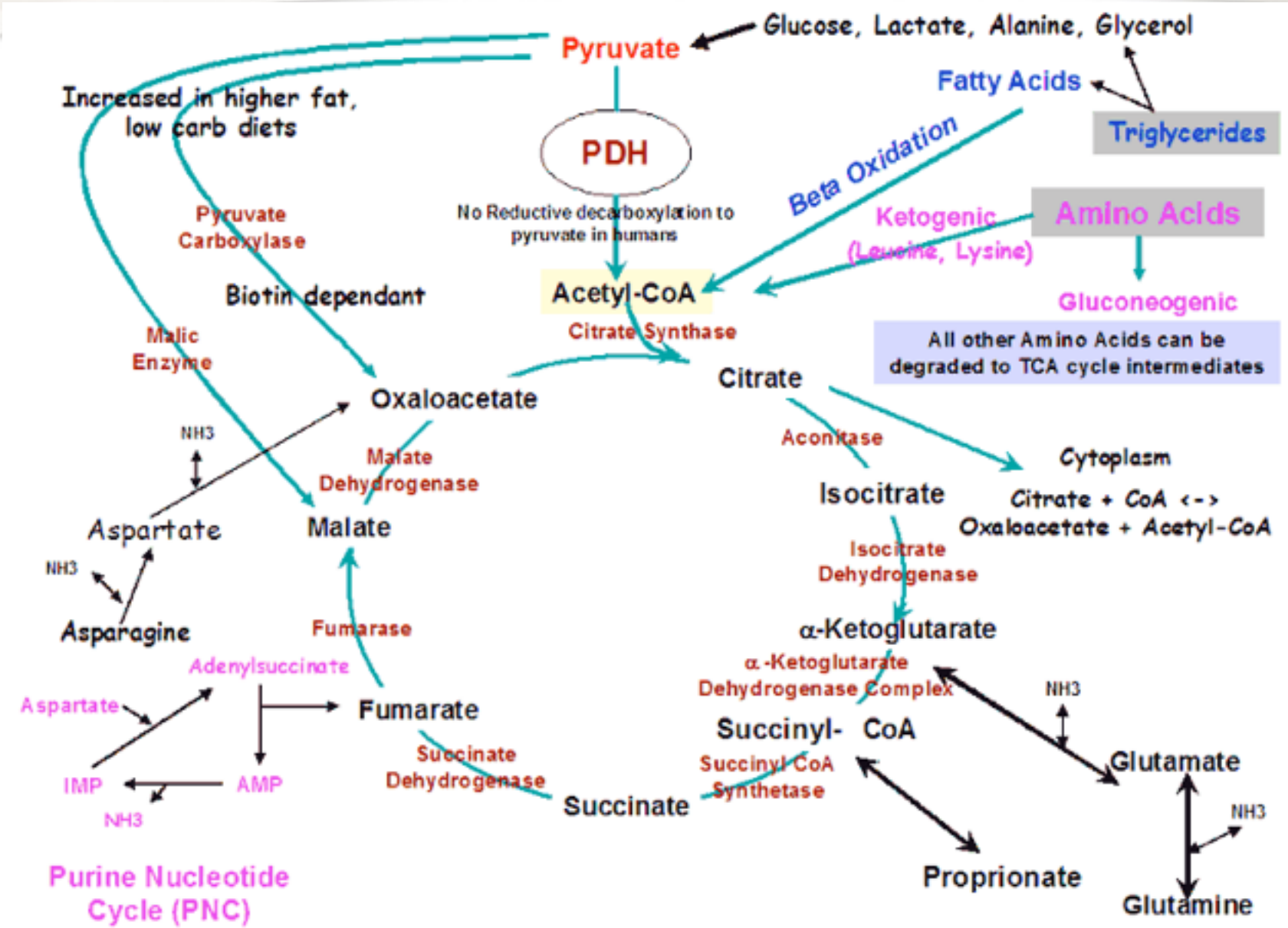
SDH mutations

- We have found mutations in all 4 SDH genes (A,B,C,D)-most of these are germline, meaning in all cells
- We have also found silencing of SDHC by "epimutation"-meaning an alteration of the DNA without changing the coding sequence
- 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

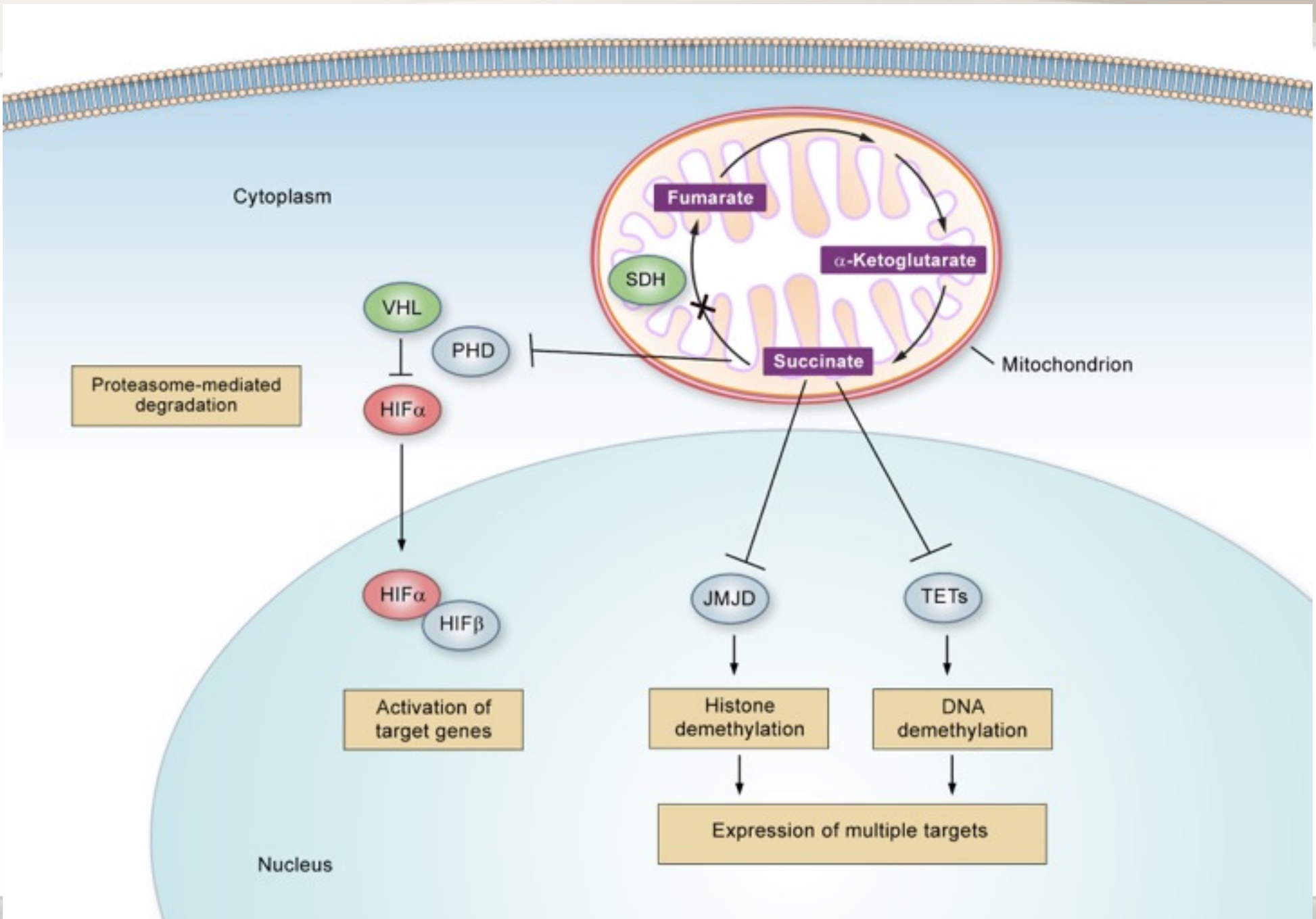
Consequences of dSDH

- **Increased succinate/αKG ratios due to dSDH inhibits αKG dependent dioxygenase catalyzed reactions:**
  - TET2 ⊣ global DNA hypermethylation
  - PHD ⊣ pseudo hypoxic state due to accumulation of HIF-1α thru blockade of HIF prolyl hydroxylation
  - Histone demethylase JMJD3 ⊣ histone methylation

Krebs Cycle


Glucose, Lactate, Alanine, Glycerol
Pyruvate
Fatty Acids
Triglycerides
Increased in higher fat, low carb diets
PDH
No Reductive decarboxylation to pyruvate in humans
Beta Oxidation
Pyruvate Carboxylase
Ketogenic (Leucine, Lysine)
Amino Acids
Biotin dependant
Acetyl-CoA
Gluconeogenic
Malic Enzyme
Citrate Synthase
All other Amino Acids can be degraded to TCA cycle intermediates
Oxaloacetate
Citrate
NH3
Aconitase
Malate Dehydrogenase
Cytoplasm
Isocitrate
Citrate + CoA <-> Oxaloacetate + Acetyl-CoA
Aspartate
Malate
NH3
Isocitrate Dehydrogenase
Asparagine
Fumarase
α-Ketoglutarate
Adenylsuccinate
α-Ketoglutarate Dehydrogenase Complex
NH3
Aspartate
Fumarate
Succinyl- CoA
Succinate Dehydrogenase
Glutamate
IMP
AMP
Succinyl CoA Synthetase
NH3
Succinate
Proprionate
Glutamine
NH3
Purine Nucleotide Cycle (PNC)

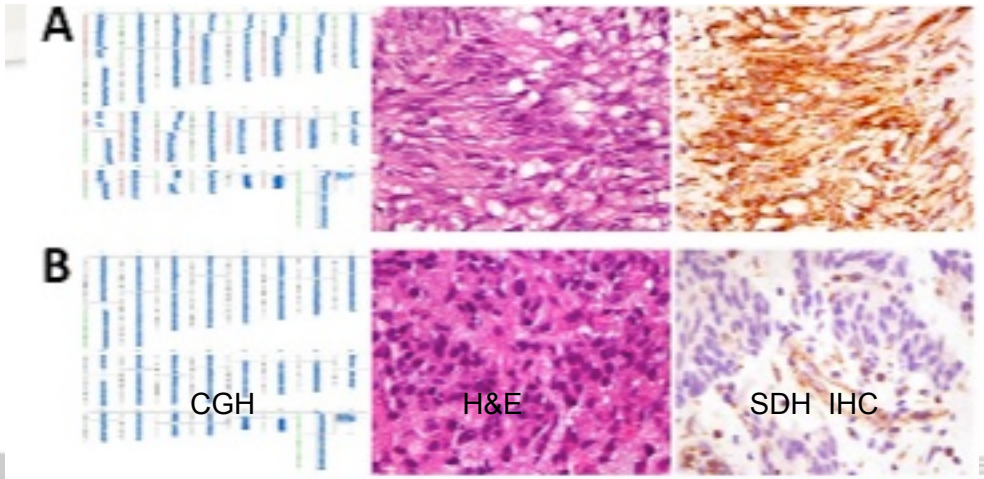
SDH Deficiency Leads to Blockade of αKG Catalyzed Reactions



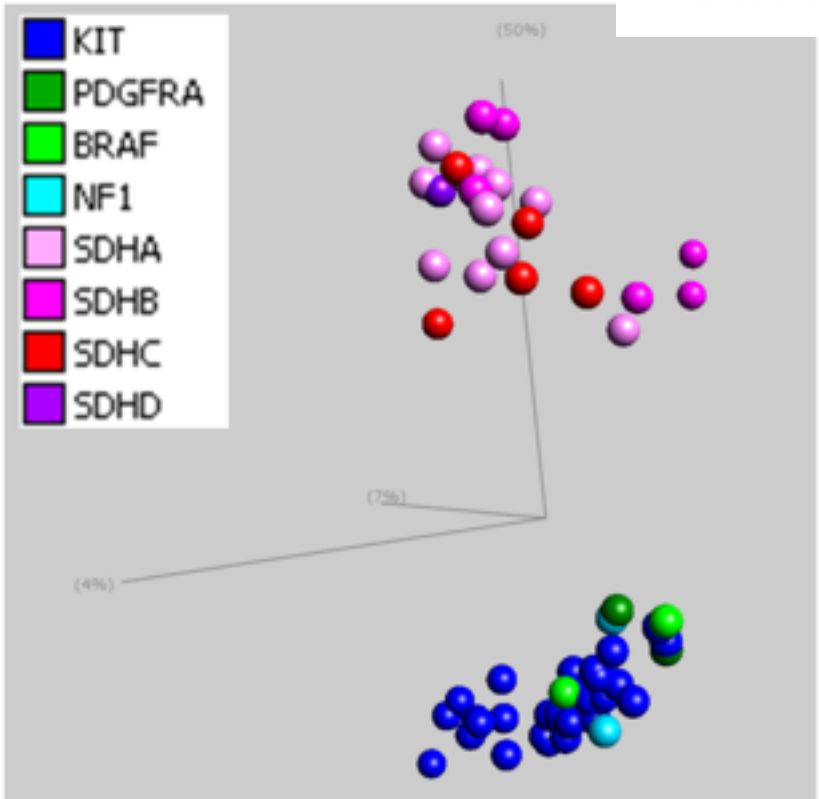
SDH-deficient GIST tumor are globally hypermethylated and stable genomes

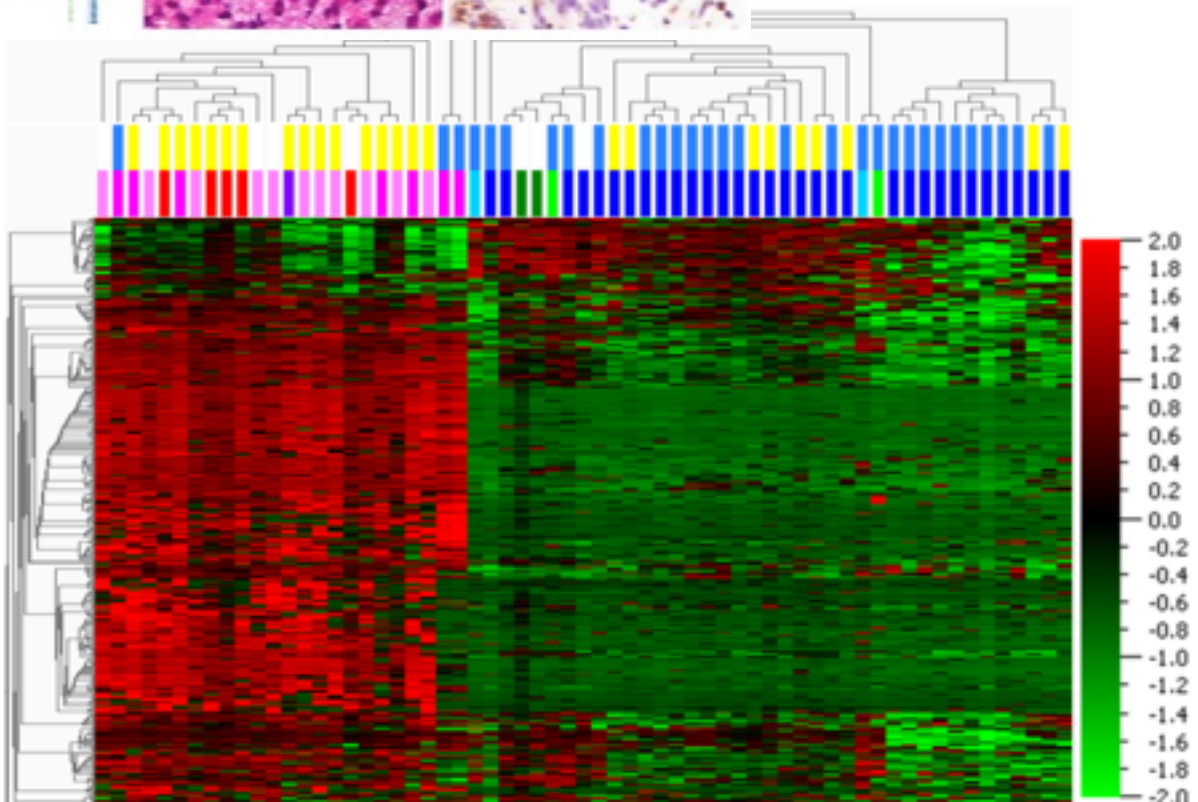
KIT Mutant GIST

SDH Mutant GIST



Killian K et al.
Cancer Discovery 2013





Future Directions

- **Continue to accrue patients with dSDH GIST**
  - Study genotype/phenotype correlations
  - We are still learning (SB dSDH GIST just discovered)
- **Accrue more patients with NF-1 GIST**
  - Determine role of Mek inhibitors in treatment
- **Based on increased succinate/αKG ratios → global DNA hypermethylation + PHD inhibition "pseudo-hypoxic" state:**
  - Test more potent VEGF inhibitors (completed testing Vandetanib)-unfortunately no activity
  - Test more potent DNMT inhibitors, e.g., SGI-110 (guadecitabine) about to open

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

Sosipatros A. Boikos, MD; Alberto S. Pappo, MD; J. Keith Killian, MD, PhD; Michael P. LaQuaglia, MD; Chris B. Weldon, MD; Suzanne George, MD; Jonathan C. Trent, MD, PhD; Margaret von Mehren, MD; Jennifer A. Wright, MD; Josh D. Schiffman, MD; Margarita Raygada, PhD; Karel Pacak, MD, PhD; Paul S. Meltzer, MD, PhD; Markku M. Miettinen, MD; Constantine Stratakis, MD, DSci; Katherine A. Janeway, MD; Lee J. Helman, MD