GIST – A complex group of related tumors with different pathogenesis and therapy

- KIT/PDGFRα mutant GISTs (85-90%)
  - Kinase inhibitor therapy, Imatinib and others
- BRAF-mutant GISTs (<1%)
  - Vemurafenib and others
- NF1/RAS pathway-associated GISTs (2-3%)
  - Salisarib
- SDH-deficient GISTs (4%)
- Quadruple wild-type GISTs - (2-3%)

GIST encompasses these categories

- Most historical GI smooth muscle tumors: leiomyomas, leiomyoblastomas, and leiomyosarcomas
- Gastrointestinal autonomic nerve tumors (GANTs)
- Many tumors previously called GI neurofibromas and schwannomas
Reclassification of archival leiomyomas and leiomyosarcomas to GISTs and true smooth muscle tumors (AFIP)

Leiomyoma vs. GIST

Leiomyosarcoma vs. GIST gross

Occurrence of GISTs - Incidence

- 14-20 per million
  Sweden, Iceland, Netherlands
- Very small GISTs are even more common
  Autopsy data: 23% frequency in the stomach
  GE-junction carcinoma specimens: 10% Harbor a GIST
Occurrence of 3461 GISTs at different sites (AFIP 1970-1996)

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Esophagus</td>
<td>0%</td>
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<tr>
<td>Stomach</td>
<td>51%</td>
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<tr>
<td>Small intestine</td>
<td>30%</td>
</tr>
<tr>
<td>Colon</td>
<td>7%</td>
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<tr>
<td>Rectum</td>
<td>7%</td>
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<tr>
<td>Abdomen</td>
<td>4%</td>
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<tr>
<td>Retroperitoneum</td>
<td>1%</td>
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<tr>
<td>Primarily disseminated GISTS</td>
<td>4%</td>
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KIT immunoreactivity in most GISTs (97%)

GIST - Problems in KIT immunohistochemistry

- **False negative**
  - Use internal positive control to validate staining adequacy
  - Epitope retrieval gives more sensitive detection

- **False positive**
  - Inappropriately high polyclonal antibody dilutions
  - Adjust to show positive Cajal and mast cells but negative muscle and fibroblasts

Anoctamin-1 (DOG1)

- A new GIST marker (97% positive)

Gene discovered in GIST (DOG1) van de Rijn, West
HUGO Name: ANO1 Protein Ano-1
Also called TMEM16A, FLJ10261, ORAOV2 (oral Carcinoma), TAOS2
Calcium-activated chloride-channel protein
- Expressed in Cajal cells, many epithelial cells, including some GI epithelia
  - Typically expressed in GISTs (97% overall)
    - Membranous and cytoplasmic patterns
    - Also in many carcinomas (Esp. squamous cell)
    - Occasional synovial sarcomas, leiomyomas
- Recommend clone K9 (most sensitive available)
- Not mutated in GIST
Differential diagnosis for KIT-positive tumors

- Angiosarcoma
- Ewing sarcoma
- Malignant melanoma
- Mastocytoma and extramed. myeloid tumor
- PEComa
- Seminoma/dysgerminoma
- Small cell carcinoma (metastatic)

Male 13 yrs, cecal mass

- Operated for a cecal mass, 2.5 cm
- Ulcerated, polypoid mass removed by partial colectomy
- Tumor reported as a GIST and referred to pediatric GIST clinic
- KIT-positive, 0 mitoses/50 HPFs
- No KIT, PDGFRA, or BRAF mutations detected
Differential diagnosis for KIT-negative tumors

- Desmoid
- Calcifying fibrous tumor
- Dedifferentiated liposarcoma
- GI clear cell sarcoma/malignant GNET
- Plexiform fibromyxoma
- Sarcomatoid carcinoma and mesothelioma
- Schwannoma
- Solitary fibrous tumor
- Synovial sarcoma

Gastric GISTs with non-malignant features
**Gastric GISTs with sarcomatous features**

**Histologic features of small intestinal GISTs**

**GIST prognosis - Assessment of biologic potential**

Division into benign and malignant more difficult than for smooth muscle tumors

GISTs form a continuum in biologic potential

Assessment of biologic potential to quantify metastatic risk
Gastric GISTs have much better prognosis than comparable small intestinal GISTs categorized by tumor size and mitotic activity (AFIP series)

KIT/PDGFRα mutational activation is Pathogenetic mechanism for most GISTs (>85%)

- Mutation causes structural change of protein leading to self-activation (phosphorylation) of the KIT/PDGFRα tyrosine kinase
- Activated KIT/PDGFRα activates KIT/PDGFRα signaling pathway
- This leads to activation of nuclear transcription factors promoting cell proliferation and decreasing apoptosis

KIT signaling networks

Proof of pathogenetic role of KIT mutations in GIST

- Mutation renders receptor a phosphorylated status
- Introduced mutations induce proliferation in cell lines
- Introduced mutations cause GISTs in mouse models
- Germline KIT mutations cause familial GIST syndrome
- Reversal of KIT activation stops cellular proliferation in vitro and vivo
**KIT already mutated in smallest GISTs**

(Corless et al.)

- What makes them grow and progress?
  - Aurora Kinase activation (Coindre et al)
  - PIK3CA mutations?

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**Clinical correlation of KIT mutations in GIST**

- Most mutations are somatic (in tumor cells only)
- 20+ families reported with heterozygous germline KIT mutations resulting in familial GIST syndrome
- Tumors with exon 11 substitution mutants have a better prognosis than deletion mutants (Stomach)
- Exon 11 internal tandem duplications are specific for gastric GISTs and correlate with better prognosis
- Exon 9 mutants occur in intestinal GISTs only and have a poor response to imatinib (Dose escalation to 800mg)

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**Imatinib response and developing resistance**

Rare mutations appear homozygous by direct sequencing

Allelic loss (hemizygosity) + duplication of mutant allele (somatic equivalent of uniparental isodisomy)

Can develop during disease progression

Poor prognosis (“double dose of mutation”)
**PDGFRA mutant GISTs**

- PDGFRA is a receptor tyrosine kinase highly homologous to KIT
- 7-10% of all GISTs are PDGFRA mutated
- Mostly gastric GISTs
- Link with epithelioid histology
- PDGFRA immunohistochemistry not diagnostically useful
- KIT/PDGFRA inhibitors can be applicable

**BRAF mutant GISTs V600E**

- BRAF: a non-receptor serine-threonine kinase involved in growth signaling
- Mutation frequency in GIST: <1%
- Mutations very common in cutaneous melanoma,
- Common in papillary thyroid cancer, lung cancer, non-Hodgkin lymphoma, and certain histiocytoses
- Most reported examples have been small intestinal GISTs – Both indolent and aggressive examples reported
- BRAF inhibitors studied BRAF mutant GISTs on trial basis

**PDGFRA mutant GISTs**

- Most common mutant Exon 18 D842V
  - This mutant is primarily imatinib resistant
- Other exon 18 mutations, single nucleotide substitutions and deletions
  - Exon 12
  - Exon 14

**Neurofibromatosis-1 associated GISTs**

The most common GI mesenchymal tumor in NF1 patients
Prevalence: up to 20-30% of NF1 patients, often incidental
Small intestinal GISTs, often multiple
  - Usually indolent
  - Diffuse Cajal cell hyperplasia
  - No KIT/PDGFRA mutations, but strong KIT expression
  - No succinate dehydrogenase loss
  - Pathogenesis may be related to RAS-pathway activation following loss of NF1-protein
Differential diagnosis: Familial GIST with multiple tumors
Succinate dehydrogenase deficient GISTs

- New oncogenic mechanism
- Loss of SDH-complex function
- Similar mechanism for paraganglioma (familial paraganglioma syndromes (30-40% of all extra-adrenal paragangliomas) and rare renal carcinomas (<1%)
- Identification of this group: Immunohistochemical loss of SDHB subunit
Pathogenesis of succinate dehydrogenase deficient GISTs

- 50% of cases have SDH-gene subunit loss-of-function germline mutations
- SDHA most commonly mutated (30% of all)
- SDHC, SDHB, SDHD less commonly
- Abnormal genome-wide methylation
- Epigenetic silencing of SDHC “epimutation” in cases with no SDH subunit mutations
- Second allele function lost via deletions (LOH detectable) or other mutations according to classic tumor suppressor model

Consequences of loss of succinate dehydrogenase complex in GISTs

- Tumor cells have no oxidative phosphorylation
- Glycolysis and reverse processing of Krebs cycle products is cell energy source
- Succinate accumulation activates HIF1/HIF2 alpha and pseudohypoxia signaling
- IGF1R signaling activated
Succinate dehydrogenase deficient GISTs

- All are gastric (7.5% of gastric GISTs)
- No KIT/PDGFRA mutations (“Wild type GISTs”)
- Retain strong KIT expression
- Most childhood and many young adult GISTs
- Activation of IGF1R signaling
- Carney Triad GISTs (GIST + pulmonary chondroma/paraganglioma, non-hereditary)
- Carney-Stratakis syndrome GISTs
  - Familial, germline mutations of SDH-subunits with GIST + paraganglioma

Insulin-like growth factor 1 receptor highly and selectively expressed in SDH-deficient GISTs

| Frequency of SDH-negative gastric GISTs by patient age (AFIP) – overall 7.5% of gastric GISTs |
| Age and sex of 66 patients with SDH-deficient GISTs (AFIP) |
**Molecular subsets of succinate dehydrogenase deficient GISTs**

- SDHA-mutant GISTS (35% of all)
  - SDHA most commonly mutated SDH subunit gene
  - Loss of SDHA immunoreactivity is typical
  - Older age of presentation (rare in children)

- SDHC epimutant GISTs (40% of all)
  - Earliest onset of age, mostly in children 8-16 years of age
  - No genomic mutations in SDH-complex
  - Epigenetic silencing of SDHC, non-inheritable

- SDHB, SDHC and SDHD mutant GISTs (25% of all)

**Unique morphologic features in SDH-deficient GISTs**

- Multinodular “plexiform” muscular involvement
- Epithelioid hypercellular histology
- Possible nuclear pleomorphism
- Common lymphovascular invasion (40-50%)
- Perigastric lymph node metastases
- Peritoneal micrometastases
Prognosis of SDH-deficient GISTs

- Gastric recurrences common
- Peritoneal micrometastases and lymph node metastases occur but are not detrimental
- Liver metastases occur at presentation - >40 years but long survival still common
- Rapid decline after long stable disease may occur
- Overall mortality 15-20% in long-term follow-up

The GIST - Take home message

- Careful differential diagnosis and prognostic assessment needed for therapy
- Molecular subtyping highly desirable for the same
- More research needed for treatment of RAS pathway-related and SDH-deficient GISTs