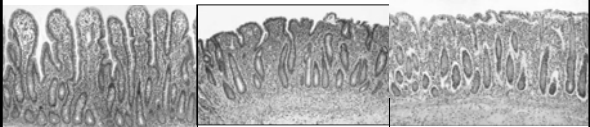


## MALABSORPTION

**Mechanisms**

1. Failure of intraluminal digestion ( ↓ peptic digestion, ↓ pancreatic enzymes, ↓ bile, bacterial overgrowth)
2. Failure of absorption (celiac sprue, tropical sprue, Whipple's disease)
3. Failure of transport (abetalipoproteinemia, lymphangiectasia)

### Celiac Disease



<b>MILD</b> (partial villous atrophy)	<b>MODERATE</b> (subtotal villous atrophy)	<b>SEVERE</b> (total villous atrophy)
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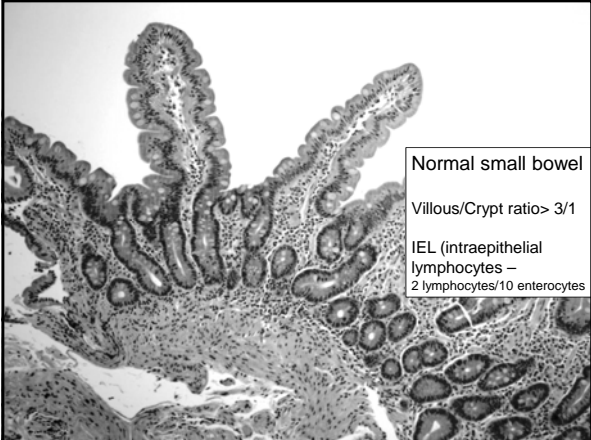
## Celiac Disease (CD)

- Autoimmune disease associated with wheat (gluten) ingestion.
- Sx: chronic diarrhea, abdominal pain, weight loss, iron deficiency anemia,
- Dx: autoantibodies to gliadin, tissue transglutaminase (tTG), reticulin, and endomysium.
- CD is strongly associated with HLA-DQ2 and HLA-DQ8 (however 40% of general population have at least one of these markers);

## CELIC SPRUE

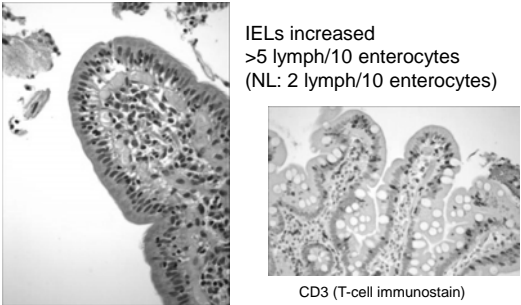
**Pathology**

**Villous atrophy**  
**Crypt hyperplasia**  
**Chronic inflammation**  
**Intraepithelial lymphocytes ↑**



**Normal small bowel**  
 Villous/Crypt ratio > 3/1  
 IEL (intraepithelial lymphocytes – 2 lymphocytes/10 enterocytes)

### Celiac Disease– Intraepithelial lymphocytosis



IELs increased  
 >5 lymph/10 enterocytes  
 (NL: 2 lymph/10 enterocytes)

CD3 (T-cell immunostain)

### Conditions with histologic overlap with Celiac disease.

#### Increased IEL

- **H. pylori gastritis**
- Viral Gastroenteritis
- Protein intolerance
- Bacterial overgrowth
- Medications
- Autoimmune enteropathy
- Tropical sprue
- Crohn's disease

#### Villous blunting

- Common variable immunodeficiency
- Viral Gastroenteritis
- Protein intolerance
- Bacterial overgrowth
- Radiation/chemotherapy
- Nutritional deficiencies
- Eosinophilic gastroenteritis
- Refractory sprue
- Tropical sprue
- Crohn's disease

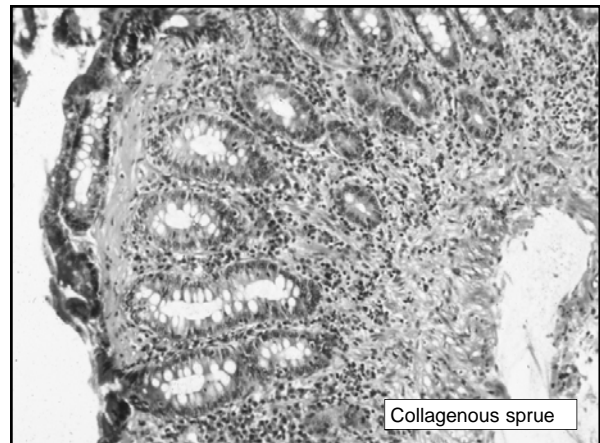
## CELIAC SPRUE

### Complications

- Collagenous sprue
- Refractory sprue
- Lymphoma
- Gastrointestinal carcinoma

## Celiac Disease: Diagnosis

- Documentation of malabsorption
- Demonstration of villous atrophy and/or intraepithelial lymphocytosis by small bowel biopsy
- Improvement of symptoms and mucosal histology after gluten withdrawal



### **Non-responsive celiac disease (NCD) (definition)**

NCD- lack of initial response to gluten free diet (GFD) or recurrence of symptoms despite maintenance of (GFD)

Diagnostic approach:

- 1) re-assess initial diagnosis of CD (presence of EMA, tTG antibodies before GFD, HLA DQ2 or DQ8 status, histology).
- 2) Assess gluten free diet (50% of NCD due to dietary gluten).
- 3) Exclude other causes of diarrhea (MC, bacterial overgrowth, IBD)

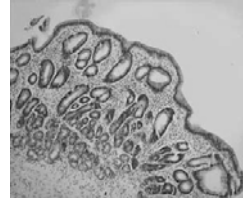
### Enteropathy-Associated T-Cell Lymphoma

- Celiac sprue-associated in most but not all cases
- Malabsorption unresponsive to gluten-free diet
- Variable gross and microscopic appearance
- Poor prognosis

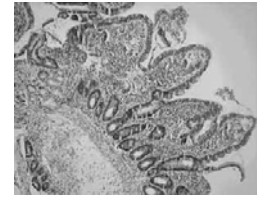
## TROPICAL SPRUE

Post-infectious sprue  
Enterotoxigenic bacteria  
(E. coli, hemophilus)  
Response to antibiotics  
Caribbean  
Central + South America  
Central + South Africa  
India

Initial biopsy



3 weeks after treatment with Doxycycline, B12 and folate.



## TROPICAL SPRUE

### Pathology

Subtotal villous atrophy  
Distal and proximal small bowel  
Patchy

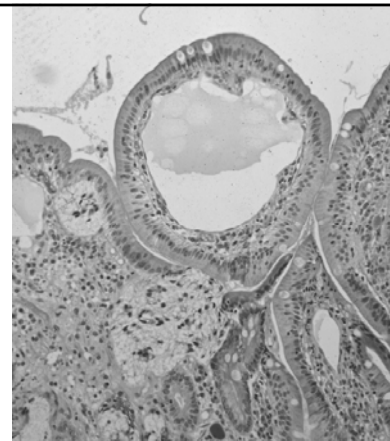
Macrocytic anemia and megalocytosis  
due to B<sub>12</sub> malabsorption

## Lymphangiectasia

- **Primary lymphangiectasia:** rare congenital disorder; defective lymphatics; normally absorbed nutrients reach the lymphatics but cannot be transported into the circulation.
- **Secondary lymphangiectasia:** more common; complication of any disorder that causes lymphatic obstruction: enlarged mesenteric lymph nodes (cancer or inflammatory), heart disease (constrictive pericarditis, CHF)

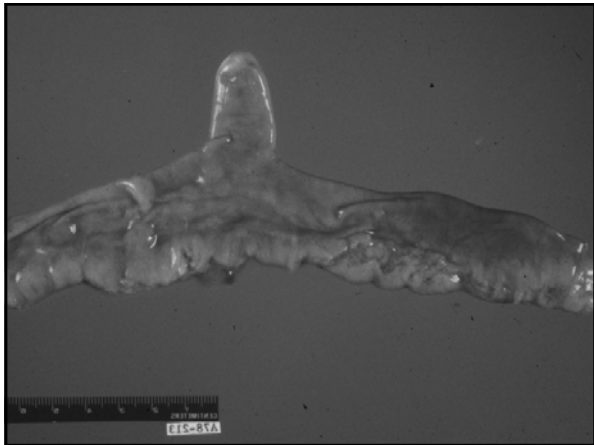
## Case Study

- 62 y male from Central America had weight loss, diarrhea and macrocytic anemia.
- The blood film showed hypersegmented neutrophils and macrocytes. His serum vitamin B12 and folate levels were low.



## Meckel's Diverticulum

- Persistence of vitelline duct (connects gut and yolk sac)- embryologic remnant – true diverticulum (all layers of bowel wall)
- "RULE OF 2s"
- 2% of normal population
- 2 ft from ileocecal valve
- Approx. 2 cm
- 50% have heterotopic mucosa; 2 types – gastric or pancreatic
- Complications: 1) inflammation (mimic appendicitis); 2) bleeding ulcer; 3) small bowel obstruction.

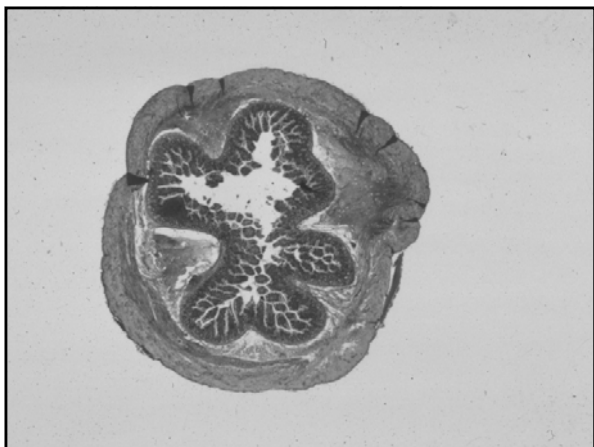


## Intussusception

- Telescoping of one segment of bowel into another
- Peristalsis propels the invaginated proximal segment farther into the distal segment
- Spontaneous in children
- Secondary to intraluminal masses in adults
- Complications: obstruction, infarction

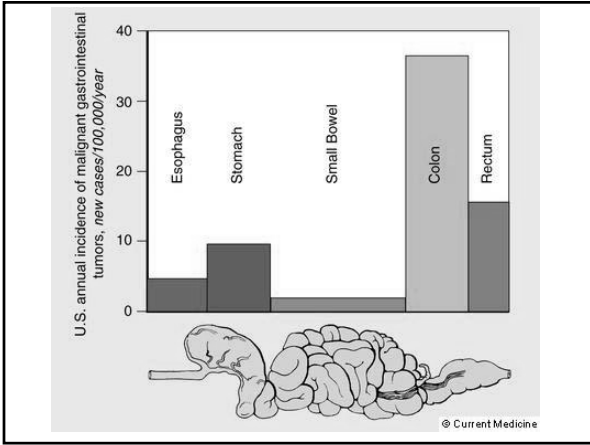
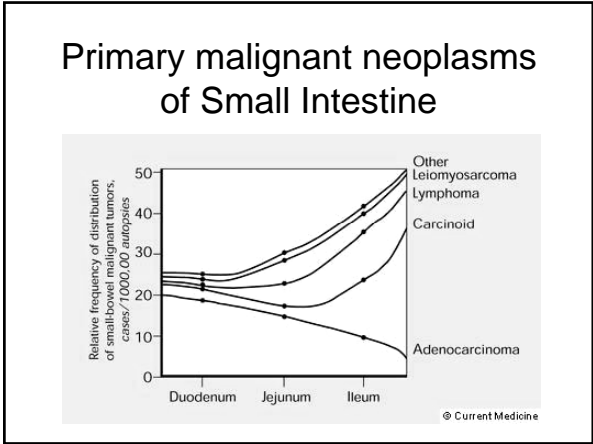
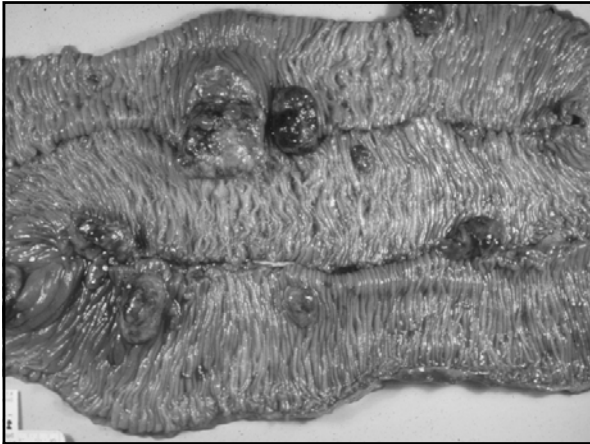
## Volvulus

- Twisting of a loop of bowel around its mesenteric base
- Sigmoid colon, cecum, small intestine, stomach, rarely transverse colon
- Complications: obstruction, infarction



## Tumors of the Small Intestine

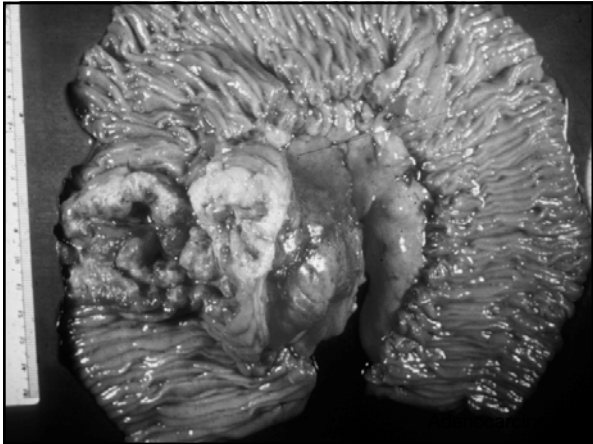
- Least frequent of all GI tumors (3-6%)
- Secondary tumors: serosal implants, direct extension from neighboring organs, distant metastases
- Primary tumors: benign tumors (often found incidentally at autopsy or surgery); malignant tumors (intestinal obstruction and bleeding)

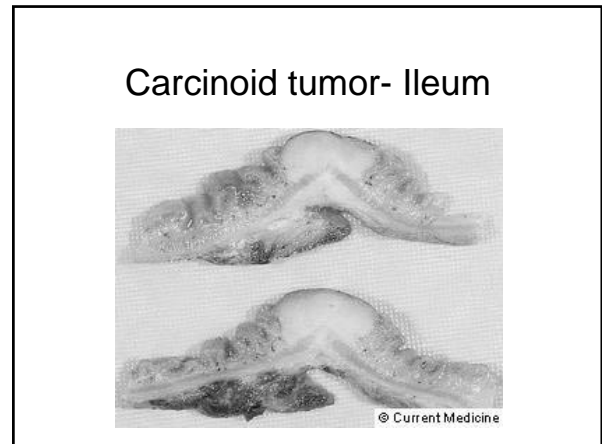
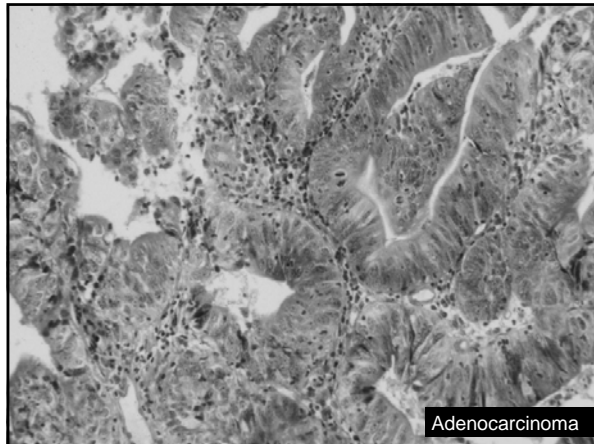


- ### Carcinomas of the Small Intestine
- Most common location: duodenum, periampullary, least common: ileum
  - Growth patterns: annular constricting or polypoid masses
  - Symptoms: Obstruction and/or bleeding
  - Predisposing conditions: Celiac disease and Crohn's disease

### Tumors of the Small Intestine: why are they so rare?

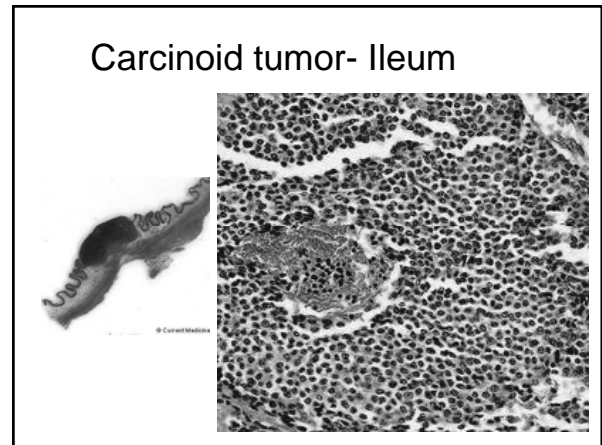
- Rapid transit of small bowel contents
- Smaller bacterial load
- Increased lymphoid tissue





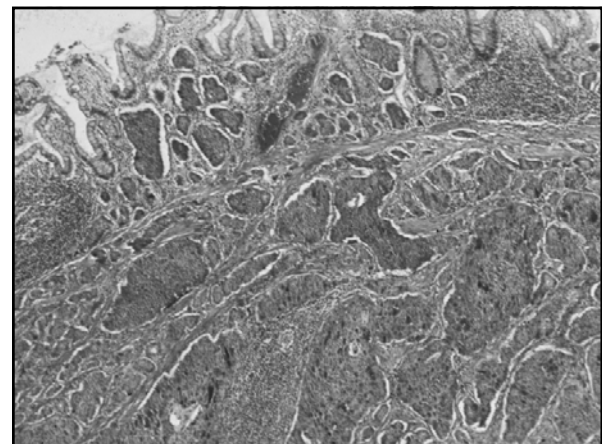
**Carcinoid Tumors of the GI Tract**

- GI tract is the most common site of carcinoids (67%)
- Small intestine is the most common site of GI carcinoids, followed by rectum and appendix
- Prognosis is SITE and SIZE dependent



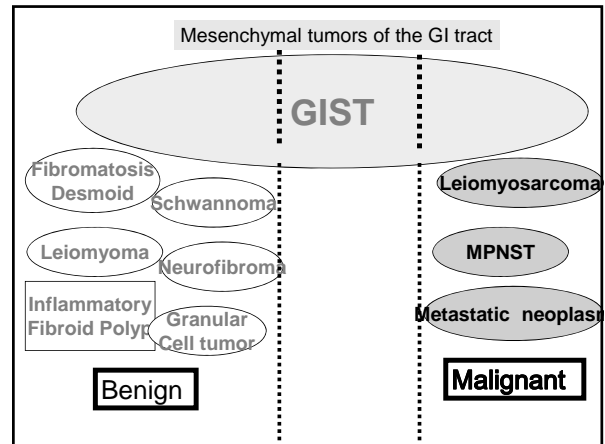
**Carcinoid tumor of the small intestine**

- Endocrine neoplasm of Kulchitsky cell origin
- Most common in ileum (80%)
- Mostly found incidentally (60-75%)
- Multicentric; slowly growing
- Gross appearance: yellow- tan nodules
- Prognosis: size and site dependent (<1cm:2% metastasis; 1-2cm:50%; >2cm:80%; best prognosis in appendix)



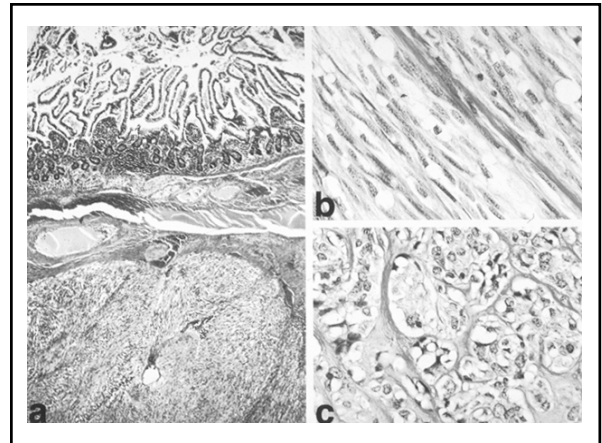
## Carcinoid tumor: Prognosis

- Much better than ordinary adenocarcinoma
- 68% 5-year survival after resection (as compared to 25-35% for adenocarcinoma)
- 38% 5-year survival after incomplete resection
- 21% 5-year survival with liver metastasis



## Carcinoid Syndrome

- Only in patients with liver metastases
- Cutaneous flushing, diarrhea, bronchospasm, right heart failure
- Serotonin, bradykinin, substance P, prostaglandins
- Elevated 5HIAA (5 hydroxy-indol-acetic acid, metabolic product of serotonin) in urin

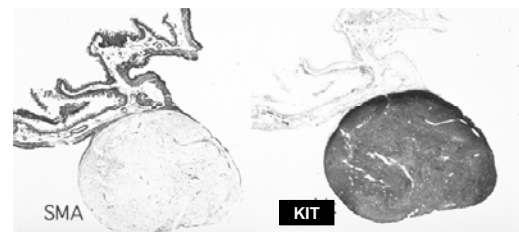


## GASTROINTESTINAL STROMAL TUMOR

Gastrointestinal Stromal Tumors (GISTs) are a distinct group of mesenchymal tumors of the GI tract.

Most common mesenchymal neoplasms in the GI tract.

GISTs have a distinctive immunophenotype.



## KIT

The *KIT* proto-oncogene encodes a type III receptor tyrosine kinase (KIT), the ligand of which is stem cell factor (SCF).

SCF-KIT interaction is essential for development of :

- Melanocytes
- Germ cells
- Mast cells
- Interstitial cells of Cajal (ICC) / gut pacemaker cells.

## KIT mutations

**Loss of function**  
(Ws/Ws mice and rats)

Defects in:  
melanogenesis  
hematopoiesis  
gametogenesis  
intestinal motility

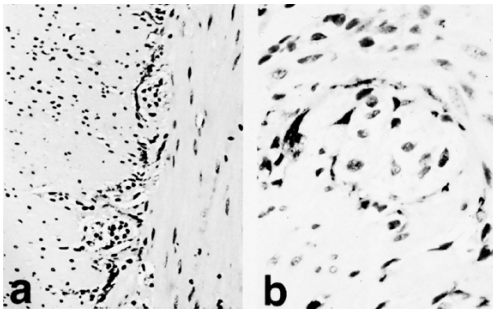
(Huizinga et al, 1995)

**Gain of function**  
(Human tumors and animal models)

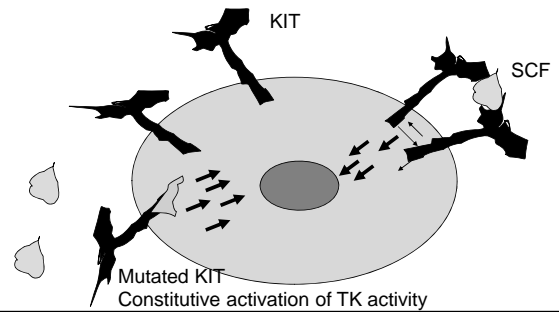
Malignant transformation in:  
Melanoma  
Mast cell neoplasms  
Gastrointestinal stromal tumors

(Nagata et al, 1992, Longley et al, 1997).

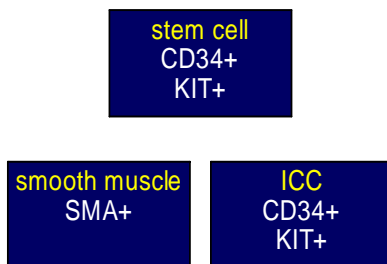
**INTERSTITIAL CELLS OF CAJAL (ICC)**  
Pacemakers cells of the gut KIT+



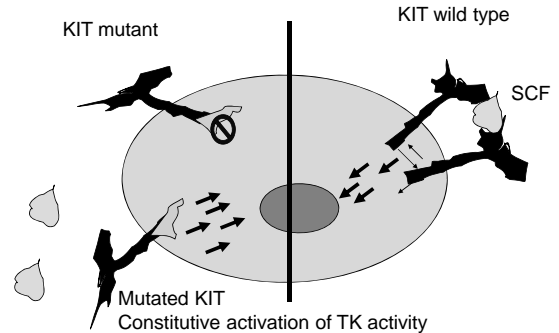
KIT receptors bind to Stem Cell Factor (SCF) leading to cross phosphorylation leading to downstream signal transduction pathways.



## Proposed GIST histogenesis



## tyrosine kinase inhibitors





## GIST Treatment

- (STI571 – Tyrosine Kinase Inhibitor)
- Gleevec, Imatinib, (Novartis, Basel Switzerland)
- Approved for treatment of CML, in which BCR-ABL tyrosine kinase is activated.
- STI 571 blocks the ATP binding site of kinase domain.
- Clinical trials for CML in 1999 showed dramatic response rates 100%. Drug was well tolerated.

1999 –in vitro studies with GIST cell lines (D.Tuveson, J. Fletcher) showed that STI571 blocked TK activity.

First GIST patient treated with STI571/Gleevec  
FDG-PET scans before and after 4 week treatment

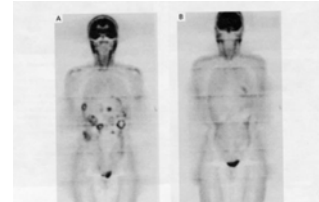


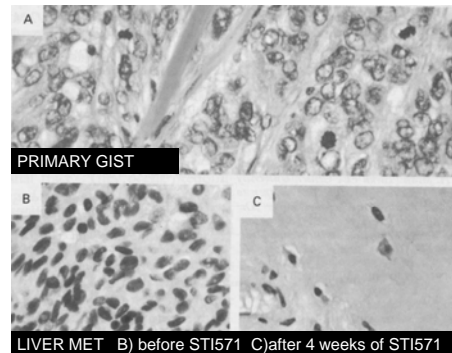
Figure 2. PET Studies with <sup>18</sup>F-Fluorodeoxyglucose in the Tumor  
Before STI571 therapy (Panel A), there were multiple metastases in the liver and upper abdomen. There was also marked resection of <sup>18</sup>F-Fluorodeoxyglucose in the right renal pelvis and ureter, a finding indicative of hydronephrosis. After four weeks of treatment (Panel B), there was no abdominal uptake of tracer in the liver or right kidney.

Joensuu H, et al. NEJM, April 5, 2001, p1052-1056.

## STI571-In vivo trial in GIST patient

First patient with metastatic GIST treated with STI571/Gleevec:  
50 yr old female with multiple recurrent, metastatic GIST.  
Multiple liver mets (>28)  
Tumor : KIT Immunoreactive  
Documented activating mutation in exon 11 of *KIT*  
Progressive disease despite all available prior therapies:  
Gastrectomy, (Mesna, Adriamycin, Ifosfamide, Dacarbazine),  
resection of mets, IFN-alpha.

. Joensuu H, et al. NEJM, April 5, 2001, p1052-1056



PRIMARY GIST  
LIVER MET B) before STI571 C)after 4 weeks of STI571  
Joensuu H, et al. NEJM, April 5, 2001, p1052-1056.

## STI571-In vivo trial in GIST patient

Tumor mets became metabolically inactive  
on PET scan.

Showed marked improvement in symptoms;  
metastases decreased in size and tumor  
showed myxoid degeneration.

Joensuu H, et al. NEJM, April 5, 2001, p1052-1056.

## Acquired STI571/Gleevec resistance in GISTs

- Majority of patients who initially benefit from tyrosine kinase inhibitors eventually become resistant.
- Median time to progression on imatinib of 2yrs.
- Mechanism of resistance – additional KIT mutation often affecting binding of drug.