

# GIST 101: The Biology of GIST



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***Disclaimer: I am not a physician. I am a biochemist with some experience in cancer research.***

- **What is GIST? What causes it? Who gets it?**
- **How are GISTs diagnosed and treated? (*in brief*)**
- **What are KIT and PDGFRA?**
- **How do “TKI” drugs (such as gleevec and sutent) work?**

# Gastro-Intestinal Stromal Tumor

- **an uncommon cancer; about 5,000 new cases per year in the USA; similar incidence worldwide**
- **a type of “sarcoma”, a rare class of cancers**
- **only about 1% of g.i. (gastrointestinal) cancers are GISTs**
- **poorly understood (and often misdiagnosed) until about 2000; rapid progress made since then**

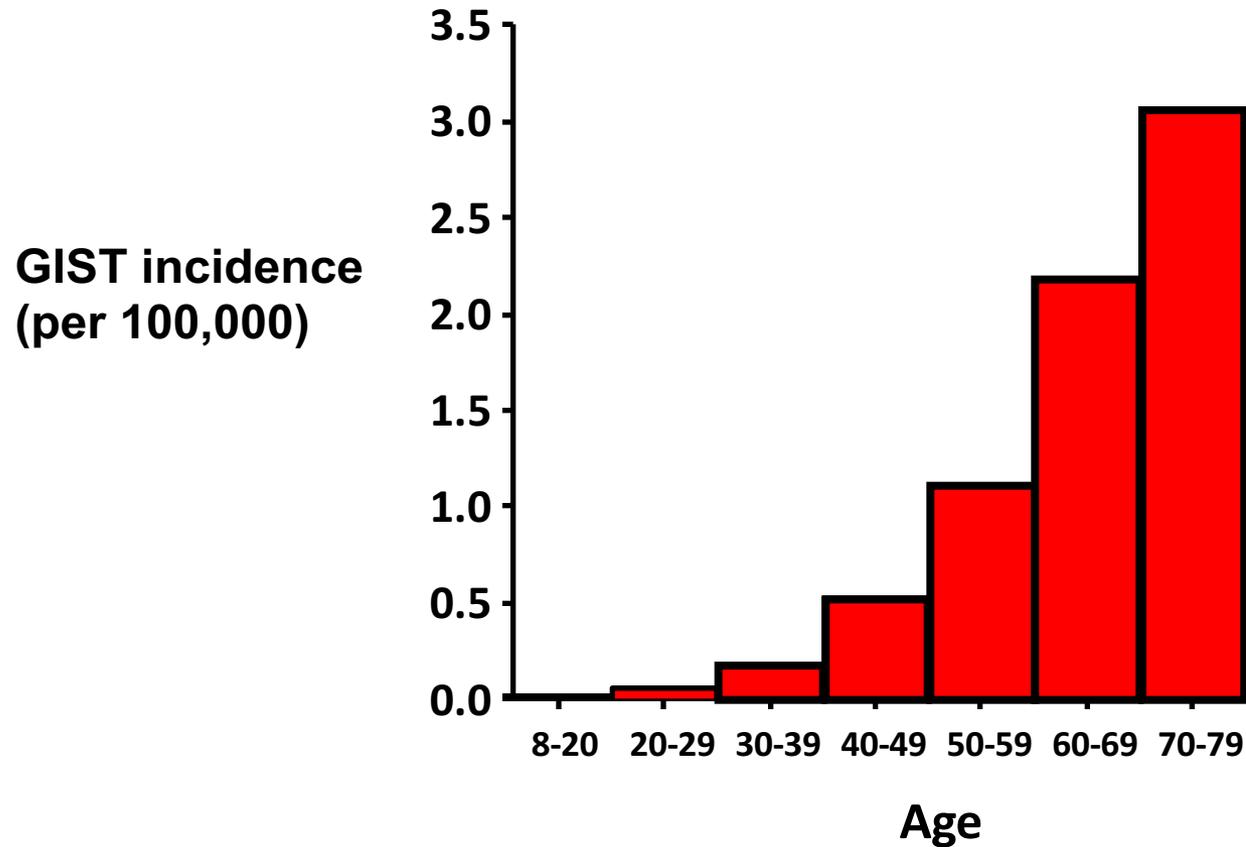
# What causes GIST?

GIST can be inherited (“running in the family”), but this is *exceedingly rare*. (I don’t know of any such cases in Canada.)

Almost all GISTs are “sporadic” (not familial) cases.  
As far as we know, *sporadic GISTs occur randomly*.

*No environmental, dietary, lifestyle, or occupational causes of GIST are known - and if there were any major risk factors, they would have been noticed by now!*

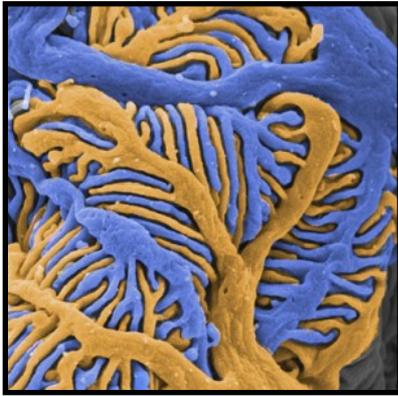
**GIST incidence increases with age,  
as is the case for most cancers.**



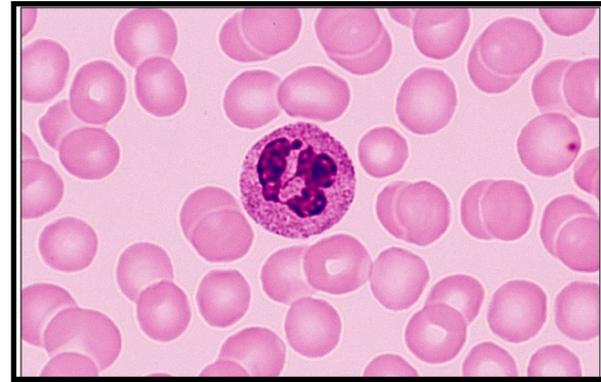
Ma et al., *Cancer Epidemiol. Biomarkers Prev.* 2014.

# ***Cells, tissues, and cancers.***

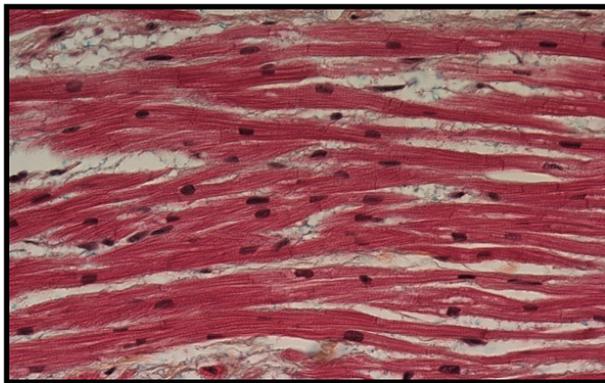
***There are hundreds of types of cells in the human body.***



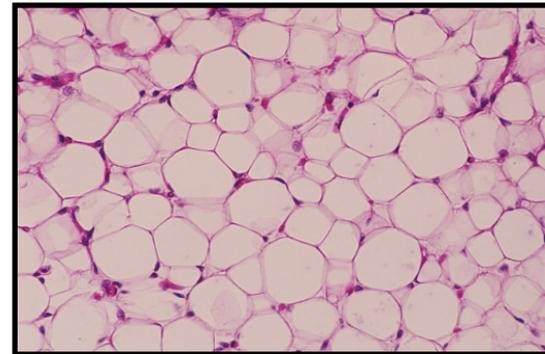
podocytes (kidney)



blood cells (red, white)



cardiomyocytes (heart)



adipocytes (fat tissue)

**Cancers can begin in almost any type of cell in the body.**

***It is the type of cell from which a cancer develops that defines the biology of the cancer. Identifying the cell type is the (extremely important!) task of the pathologist.***

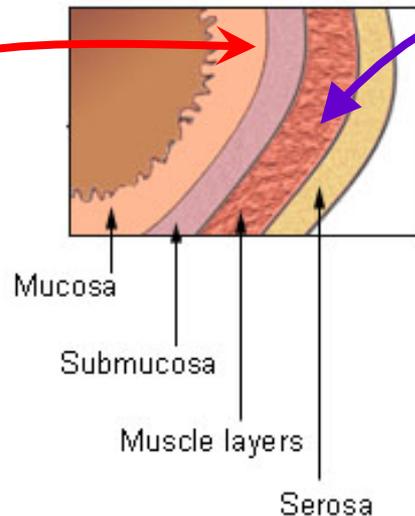
## Carcinomas and sarcomas

Most cancers are *carcinomas*, which arise in epithelial (“lining”) tissues (skin, colon, lung, bladder, prostate, breast, etc.).  
GIST is not a carcinoma; it is a sarcoma.

Sarcomas are cancers that arise from cells of connective tissues, blood vessels, cartilage, bone, etc.

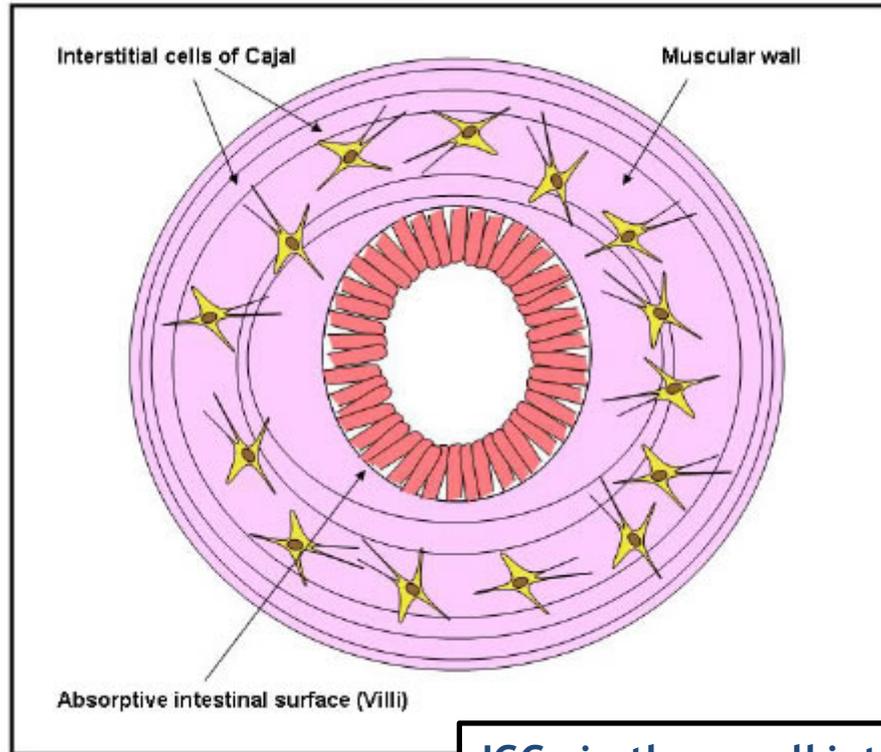
Sarcomas are rare (about 1% of all cancers).

carcinomas start on the *inside* (lining) of the g.i. tract.



GISTs start on the *outside* (muscular wall) of the g.i. tract

# ICCs: the cells where GISTs start; “Interstitial cells of Cajal”

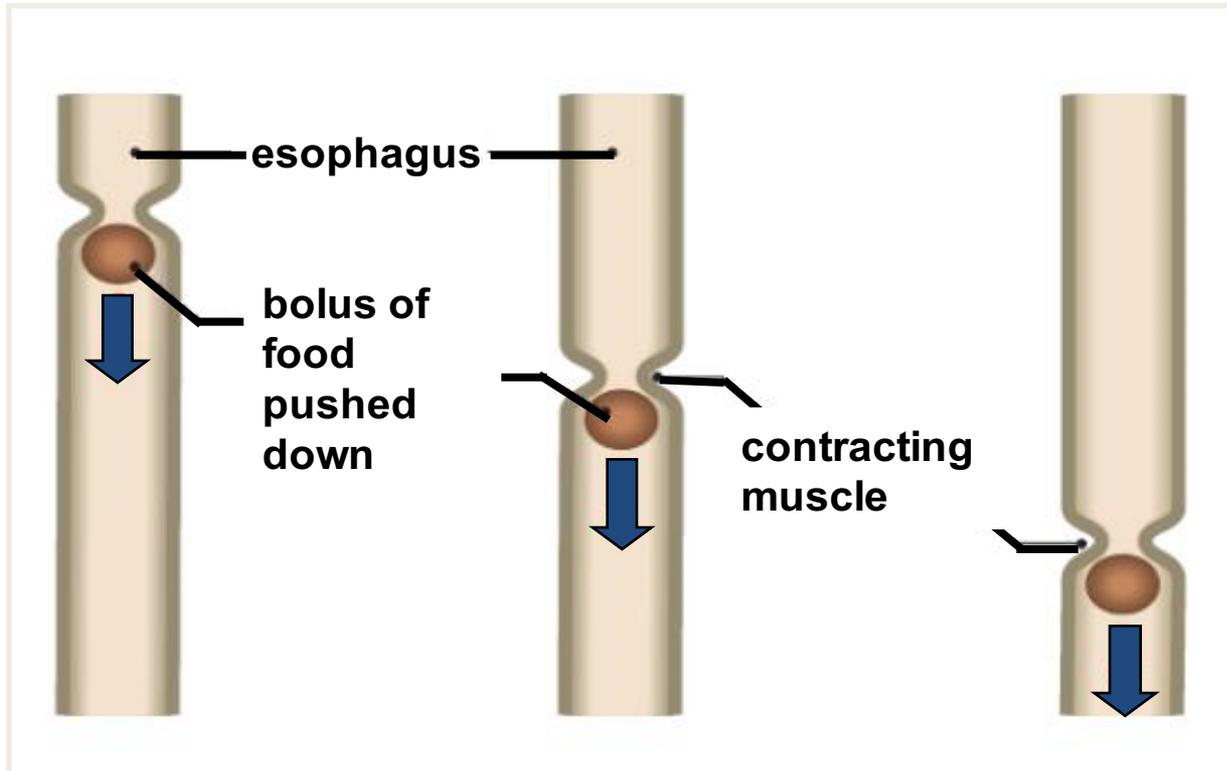


ICCs in the small intestine

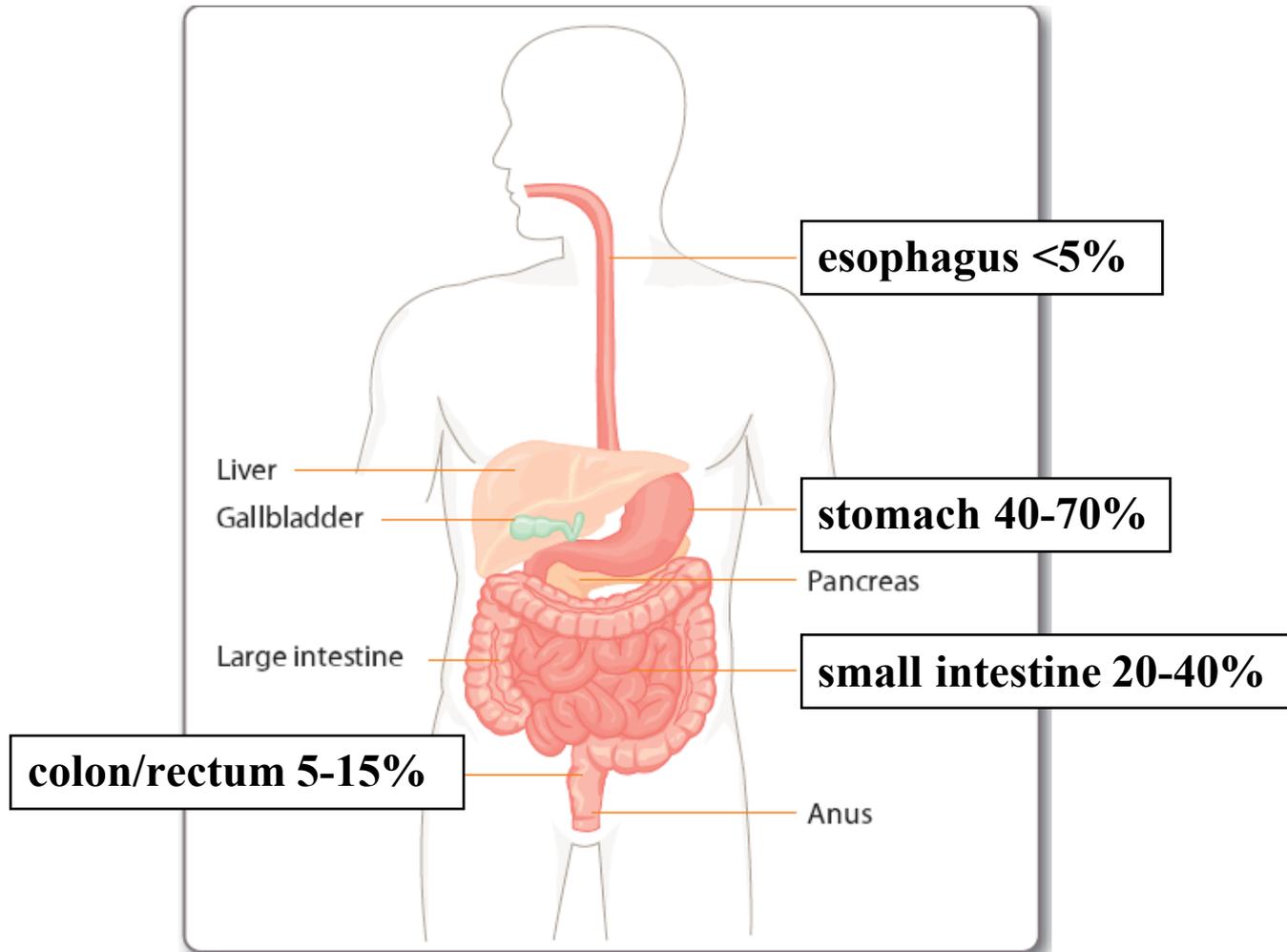


Dr. Brian Rubin, Interstitial cells of Cajal: What are they and why should you care?  
[www.liferaftgroup.org/news\\_sci\\_articles/interstitial\\_cells\\_cajal.html](http://www.liferaftgroup.org/news_sci_articles/interstitial_cells_cajal.html)

ICCs are the “pacemaker” cells that coordinate peristalsis - the waves of muscle action that push food along the g.i. tract during digestion. ICCs send out the electrical signals that stimulate the g.i. smooth muscle to contract.



All GIST tumors arise in the same cell type (ICC), regardless of their location along the GI tract.



***A GIST that starts in the stomach is a GIST***

***(... not what people are usually referring to when they say “stomach cancer” - the common adenocarcinoma).***

***A GIST that starts in the colon is a GIST***

***(... not what people are usually referring to when they say “colon cancer” - the common colorectal carcinoma).***

Like other cancers, GIST is dangerous because:

**Local growth** of the tumor may disrupt the function of the GI tract, cause internal bleeding, etc.

The primary cancer can **metastasize** - spread from the “primary” site to new - sometimes distant - sites in the body, such as the liver, lungs, or brain.

Both the cancer itself and the side effects of treatment can cause life-threatening complications, such as anemia, infections, liver damage, etc.

# Diagnosis: Symptoms of GIST

GISTs can grow surprisingly large before they produce any symptoms. There is no “typical” specific symptom of GIST.

Common symptoms include:

- abdominal “fullness”, discomfort, or pain
- palpable abdominal mass
- consequences of tumor bleeding; anemia

*Unfortunately, many common GI conditions can cause similar symptoms, so GIST diagnosis is often delayed.*

*A story that we hear far too often: “The patient is a man in his 60s living in Canada. After a whole year during which his family doctor told him that he just had “a bad case of heartburn”, he finally saw another doctor, who did further tests, including CT scan, gastroscopy, and endoscopy, and diagnosed GIST.”*

# Diagnosis; Localized vs Metastatic GIST

Once a GIST is discovered, the work of the pathologist is critical, and his/her degree of experience counts!

A GIST begins as a localized growth (“primary”); a localized GIST may be cured by surgery alone.

However, the primary GIST can **metastasize** - spread from the “primary” site to new - sometimes distant - sites in the body, such as the liver, lungs, or brain.

Even after apparently successful surgery, a GIST may recur (re-grow at the original site) or metastasize.

Once a GIST has metastasized, surgery cannot be curative: systemic therapy (usually, drug therapy) is required.

# GIST Risk Assessment

Certain clinical factors can be used to assess the risk that a localized GIST will subsequently metastasize.

*Two major factors in GIST risk assessment:*

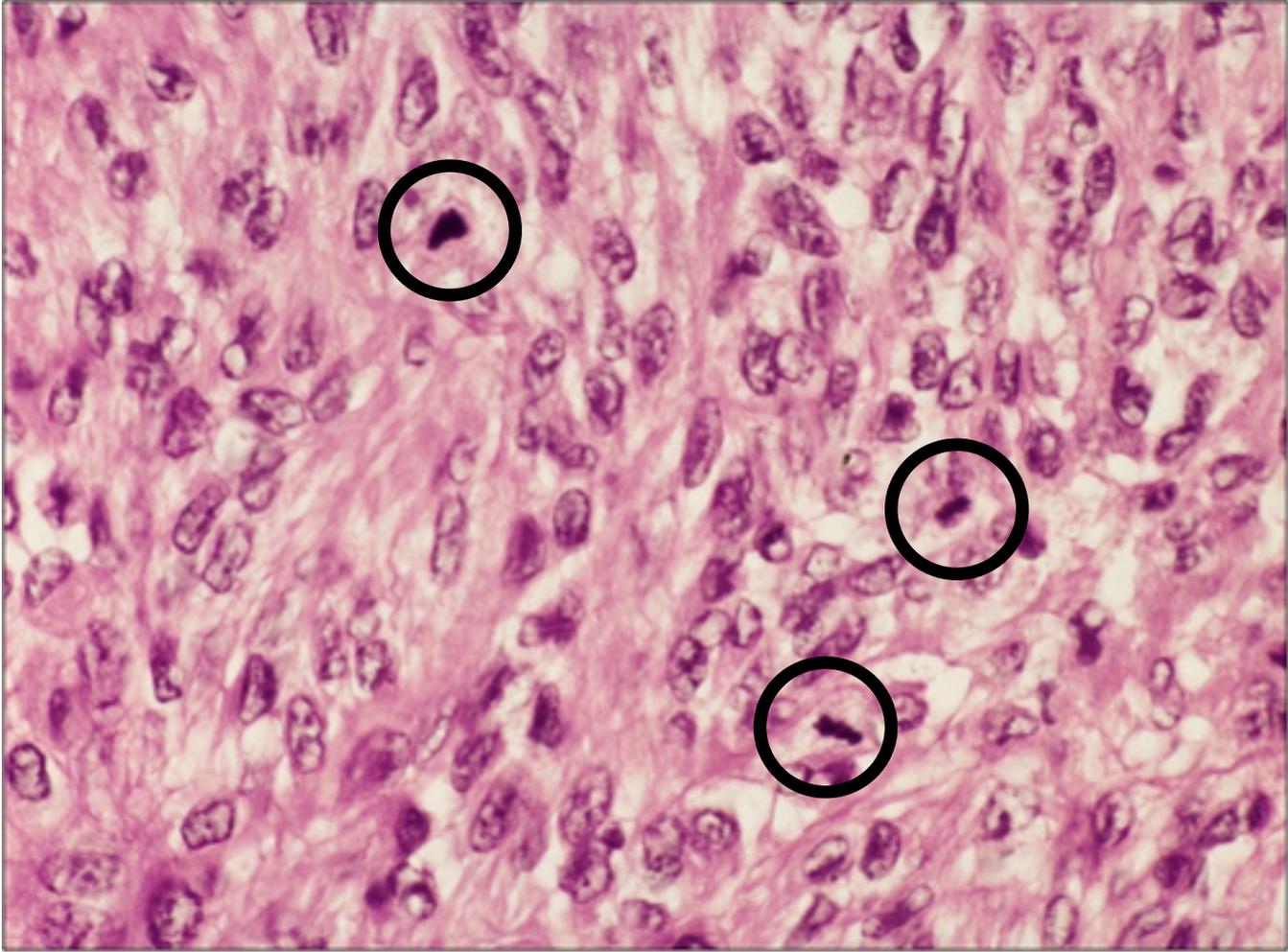
Size of the GIST at the time of diagnosis; smaller is better!

Mitotic rate (a measure of how fast the tumor is growing); the rate is analyzed by the pathologist, looking at the specimen through a microscope; lower is better!

This assessment will probably determine the recommended course of treatment, such as the decision whether to prescribe “adjuvant” imatinib (Gleevec).

*“Adjuvant” therapy: taking imatinib after surgical removal of a localized GIST, to reduce the risk of recurrence or metastasis. The medical consensus on adjuvant therapy continues to evolve; a three-year course is now typical. Adjuvant treatment is much more likely to be prescribed for high-risk GIST.*

# Counting mitotic figures (leiomyosarcoma)



**Metastases (“mets”), wherever they occur, have the biological properties of the primary tumor.**

**GIST mets in the liver, brain, or lung are still GISTs and must be treated as GISTs - *they are not liver cancers (cancers arising from liver cells), or brain cancers, or lung cancers.***

## Initial treatment for metastatic disease:

**Gleevec (imatinib)** is beneficial in >85% of cases. Often, the mets persist, but they stop growing.

After some time (months, years, decades ...), imatinib resistance may develop, and some or all of the mets may start to grow again.

## Treatment options for imatinib-resistant GIST include:

- ❖ **Surgery for limited progression**
- ❖ **Gleevec (imatinib) dose increase**
- ❖ **Sutent (sunitinib): 2<sup>nd</sup> line**
- ❖ **Stivarga (regorafenib): 3<sup>rd</sup> line**
- ❖ **Clinical trials**



may be  
combined

# Possible new treatment approaches for metastatic disease (as yet unproven)

## Immunotherapy:

Tan *et al.*, The immune system and gastrointestinal stromal tumor: a wealth of opportunities, *Curr. Opin. Oncol.* 27: 338-342, 2015.

## Monoclonal antibodies:

Edris *et al.*, Use of a KIT-specific monoclonal antibody to bypass imatinib resistance in gastrointestinal stromal tumors, *Oncoimmunology* 2: e24452, 2013.

## Radiotherapy (previously considered ineffective):

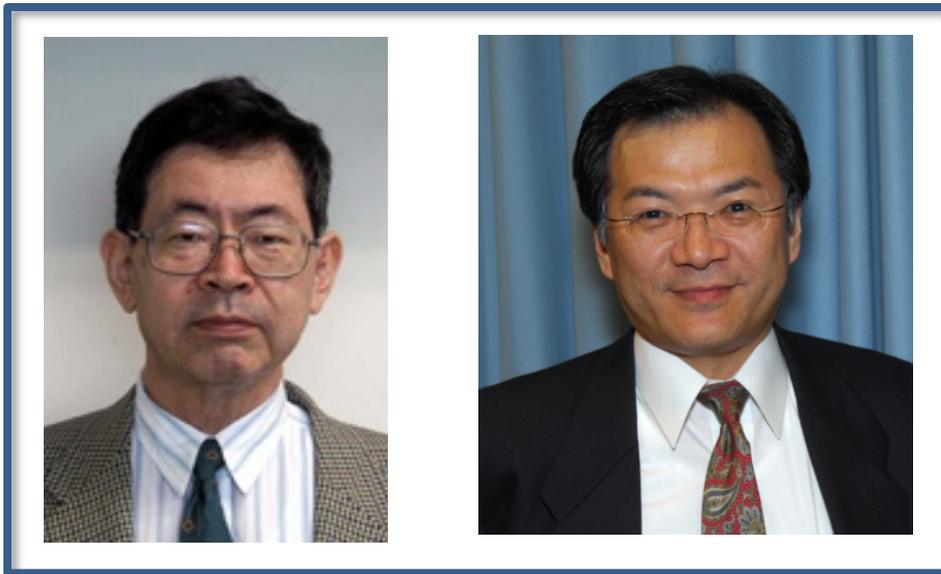
Joensuu *et al.*, Radiotherapy for GIST progressing during or after tyrosine kinase inhibitor therapy: A prospective study, *Radiother. Oncol.* 116: 233-238, 2015.

## Nuclear medicine:

Arne *et al.*, Gastrointestinal stromal tumors (GISTs) express somatostatin receptors and bind radiolabeled somatostatin analogs, *Acta Oncol.* 52: 783-792, 2012.

# GIST and the KIT protein

GIST cells express a protein called “KIT”;  
very few other cells in the body do so.



Yukihiro Kitamura, M.D.

Seiichi Hirota, M.D.

Osaka Univ. Med. School

This discovery (1998)  
revolutionized our  
understanding of GIST biology  
and treatment.

## Mutations that “drive” GIST

In about 75% of GIST cases, there is a **mutation in the *KIT* gene** (DNA), so the GIST cells express an **activated** form of KIT protein that forces the cells to keep dividing.

In another 10% of GISTs, the *KIT* gene is normal; instead, there is a mutation in a very similar gene, the “platelet-derived growth factor receptor alpha” (***PDGFRA***) gene. This was discovered in 2003.

## “Wildtype” GIST

Some GISTS do not have mutations in either the *KIT* or *PDGFRA* genes. In genetics, the “normal” (not mutant) form of a gene is called the “wild type”. So, we can call these cases “wildtype” GISTS. Really, they are just GISTS with mutations in other genes (some known and some as yet unknown). Wildtype GISTS are a small minority - rarities within a rare disease.

In 2011, it was discovered that about half of these “wildtype” GIST cases have mutations affecting a very different gene/protein, SDH (succinate dehydrogenase). These GISTS typically occur in children and young adults (“pediatric GIST”).

## It's complicated.

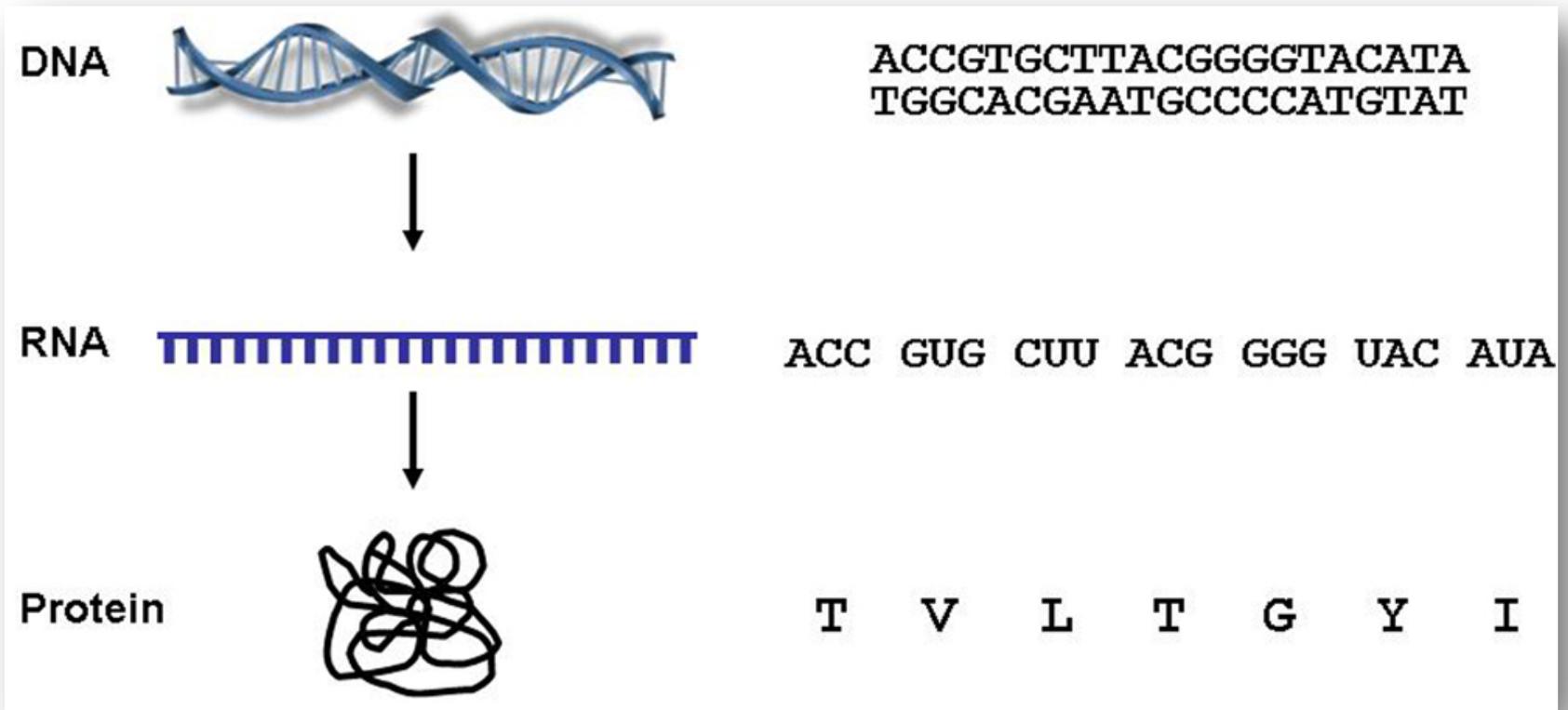
As research progresses, we are learning that GIST is really a constellation of several related diseases (perhaps ten or even more) with different molecular and clinical characteristics.

This makes GIST oncology a lot more complicated, but it is also bringing new hope that therapies can be targeted even more precisely to specific forms of GIST.

For the rest of this talk, I will focus on *KIT*-mutant GIST, which is the most common form.

# Genes and Proteins

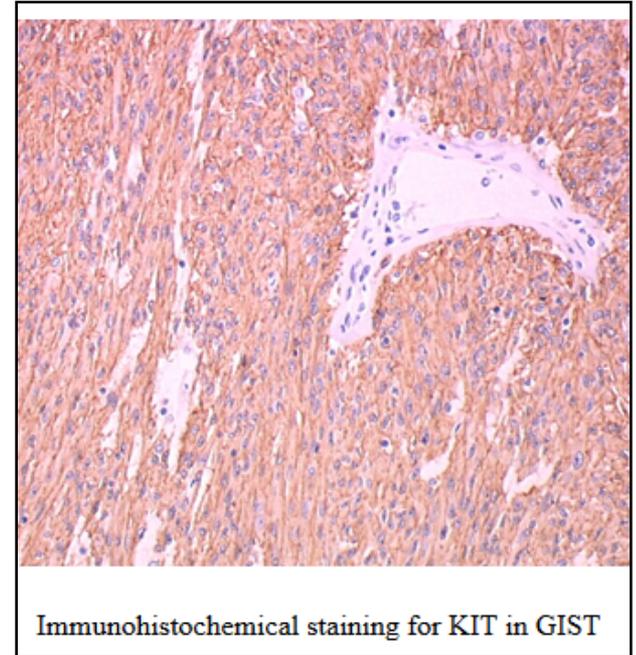
Genes (DNA) are the code (blueprints) for construction of the cell's proteins. The human genomes encodes >30,000 different kinds of proteins.



## KIT (“c-Kit” or “CD117”)

KIT is a specific protein; it is made by only a few types of adult cells, including ICCs and GISTs.

***Immunohistochemistry:*** The essential step in diagnosing GIST is to test whether the tumor cells express KIT. This is done by *staining* the tissue sample with an *antibody* that recognizes KIT.



Blay *et al.*, 2012

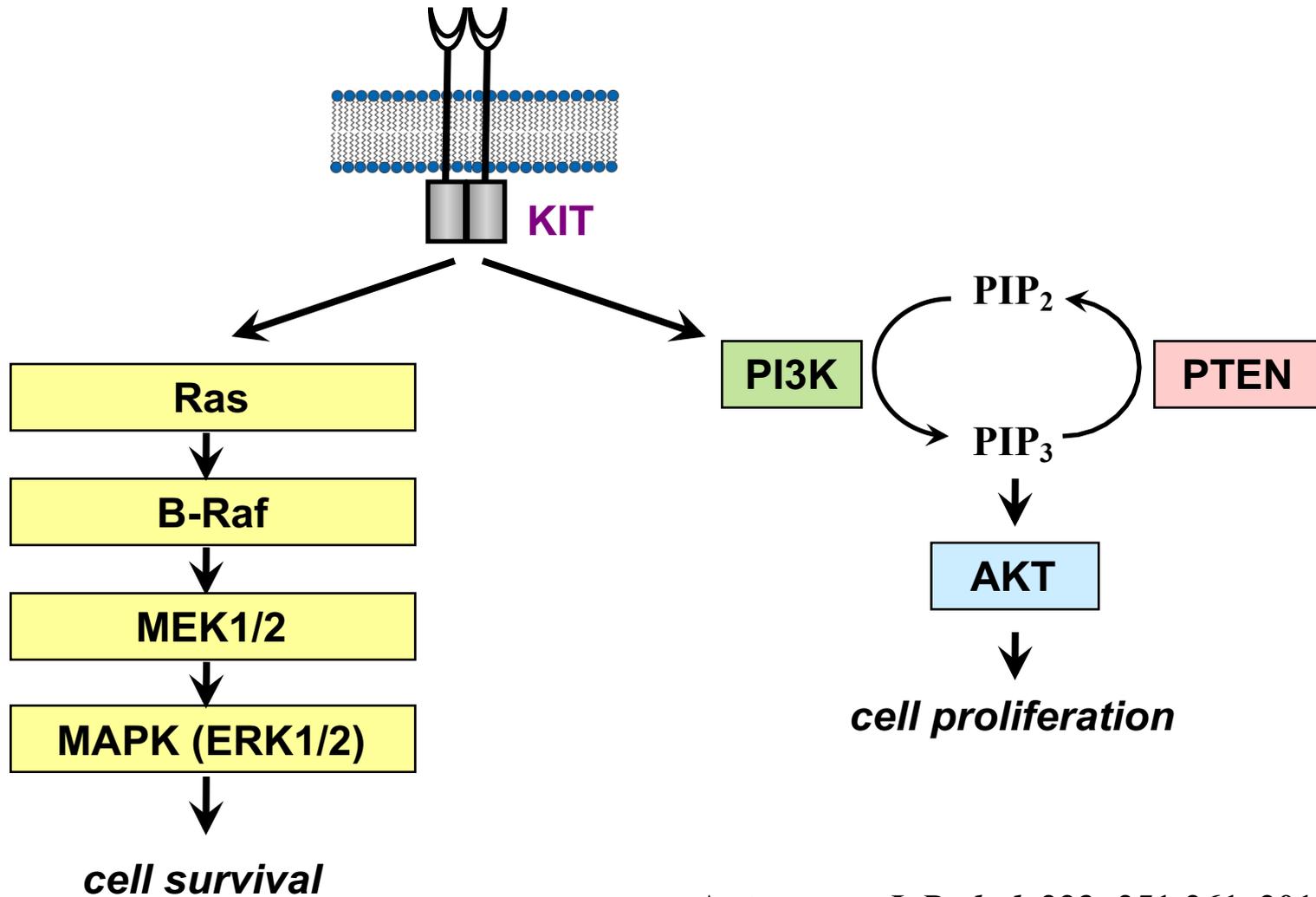
The stained tissue is examined under the microscope.

The *KIT* gene is an “oncogene”.

An oncogene is a gene that encodes a protein product which, when mutated, can instruct the cell to keep dividing: a “stuck gas pedal”.

The KIT protein is an enzyme - a “tyrosine kinase” - that acts on other proteins (signal transduction cascade).

# KIT signalling in GIST



Antonescu, *J. Pathol.* 223: 251-261, 2011.

### ***In normal ICC (pacemaker) cells:***

A “growth factor” binds to KIT (“steps on the gas pedal”). KIT becomes active and tells the cell to grow and divide - but only in response to the growth factor.

### ***In GIST cells:***

The *KIT* gene is mutated. An altered form of KIT protein is produced. This form is “always turned on” (“stuck gas pedal”), even in the absence of the growth factor. The GIST cell keeps dividing, in an uncontrolled manner.

## What is a mutation?

- Change in the DNA sequence encoding a protein.
- Mutations occur randomly, but natural selection causes cells carrying certain mutations to survive and grow preferentially.

## What does “V654A” mean?

Because of a mutation in the GIST cell’s DNA, the 654<sup>th</sup> amino acid residue (building block) in the KIT protein has changed from the normal valine (V) to a different residue, alanine (A).

For more information, see: “Mutations and Mutation Testing” on the Life Raft Group USA web site.

**The mutations in GIST tumors are almost always *somatic* - not *germline* - mutations.**

- occurring in cells of the body during development or adulthood, but not affecting germ cells (egg or sperm cells)
- the somatic KIT mutation is carried by all of the tumor cells, but it cannot be passed on to a patient's children

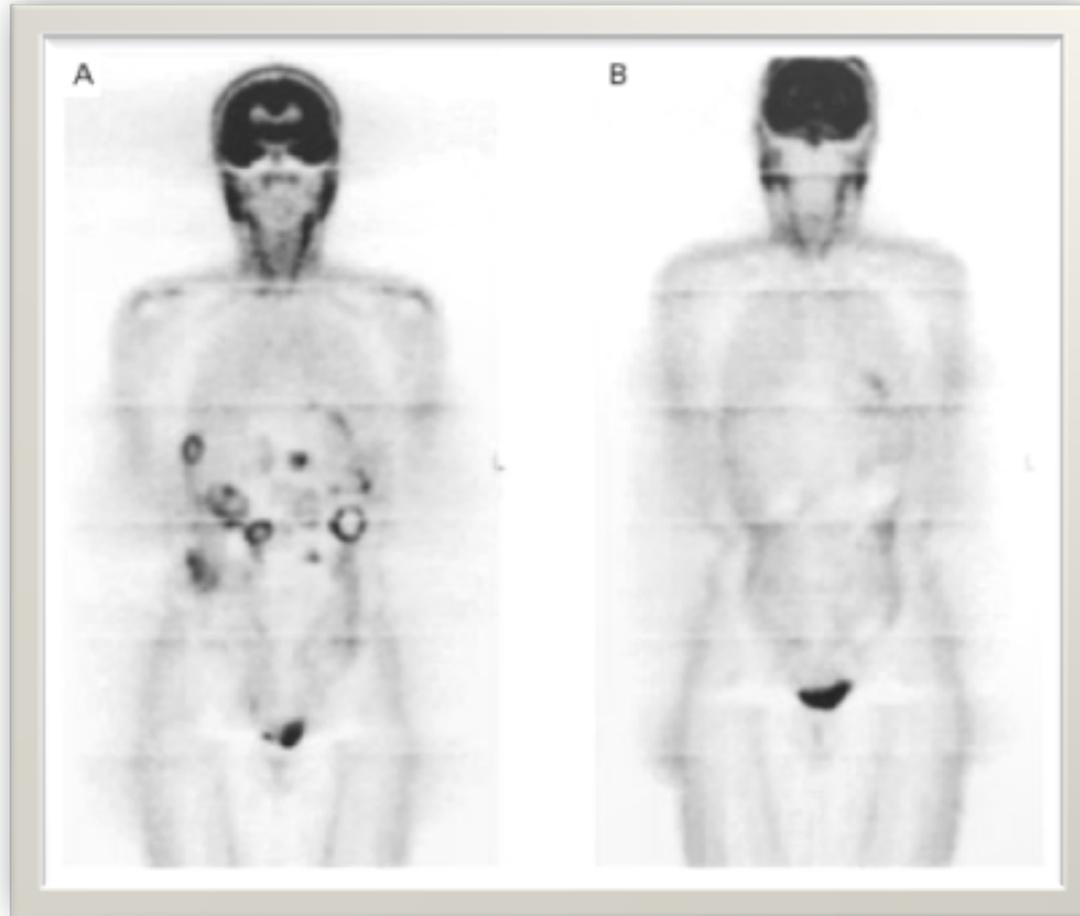
**Mutations in GISTs can arise in many different sites within the *KIT* gene, affecting many different sites within the KIT protein.**

**The site of the mutation influences the biology of the disease:**

- anatomical site**
- prognosis**
- drug response**

**Mutation testing should be performed on all new GIST cases (Baveno declaration, 2008).**

# The development of targeted drugs for treating GIST



**Joensuu *et al*, *N. Engl. J. Med.* 344: 1052-1056, 2001.**

Many drugs are “small-molecule” enzyme inhibitors.

Small molecules:

*Synthesized in the lab:* not “biologicals” (antibodies, vaccines, proteins, etc.) produced by cells

*Orally bioavailable:* can be taken as pills

*Enzyme inhibitors:* chemical compounds that shut down the action of a particular enzyme

*Examples:*

- methotrexate (dihydrofolate reductase)
- ritonavir (HIV protease)
- sildenafil/viagra (phosphodiesterase)
- celebrex (cyclooxygenase 2)

# The development of targeted drugs for treating GIST

## Chronic Myelogenous Leukemia (CML)

A rare leukemia (cancer of the blood) that looks completely different from GIST ... but the two diseases turned out to be related, at the molecular level.

The mutation causing CML is in a gene called “ABL”; this was discovered in 1985.

**ABL is a “tyrosine kinase” enzyme. Drugs that shut down those enzymes are “tyrosine kinase inhibitors” (TKIs). Can TKIs shut off the growth of the leukemia cells?**

The 2009 Lasker-DeBakey Clinical Medical Research Award honors three scientists who developed novel treatments for chronic myeloid leukemia that converted this fatal cancer into a manageable chronic condition. [They] broke new ground in cancer therapy and radically altered the prognosis of CML patients.



**Brian J. Druker**  
Oregon Health & Science  
University

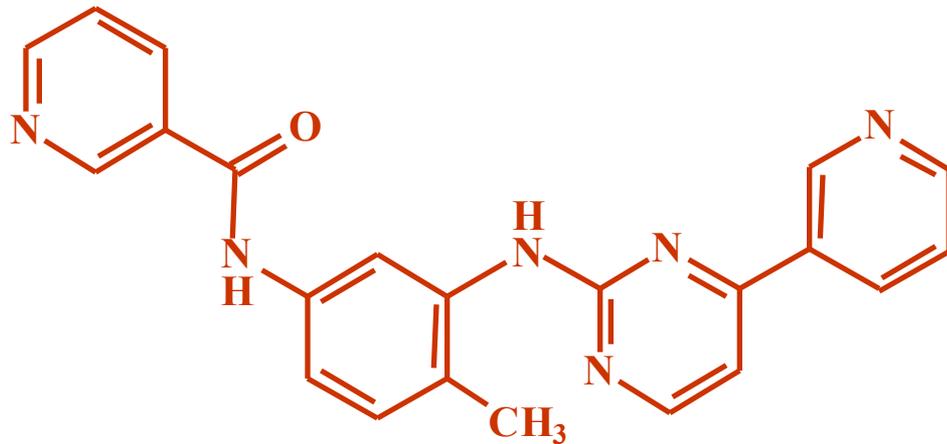


**Nicholas B. Lydon**  
Formerly of Novartis



**Charles L. Sawyers**  
Memorial Sloan-Kettering  
Cancer Center

# Gleevec (STI571; imatinib) inhibits ABL



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# Magic Cancer Bullet



How a Tiny Orange Pill Is  
Rewriting Medical History

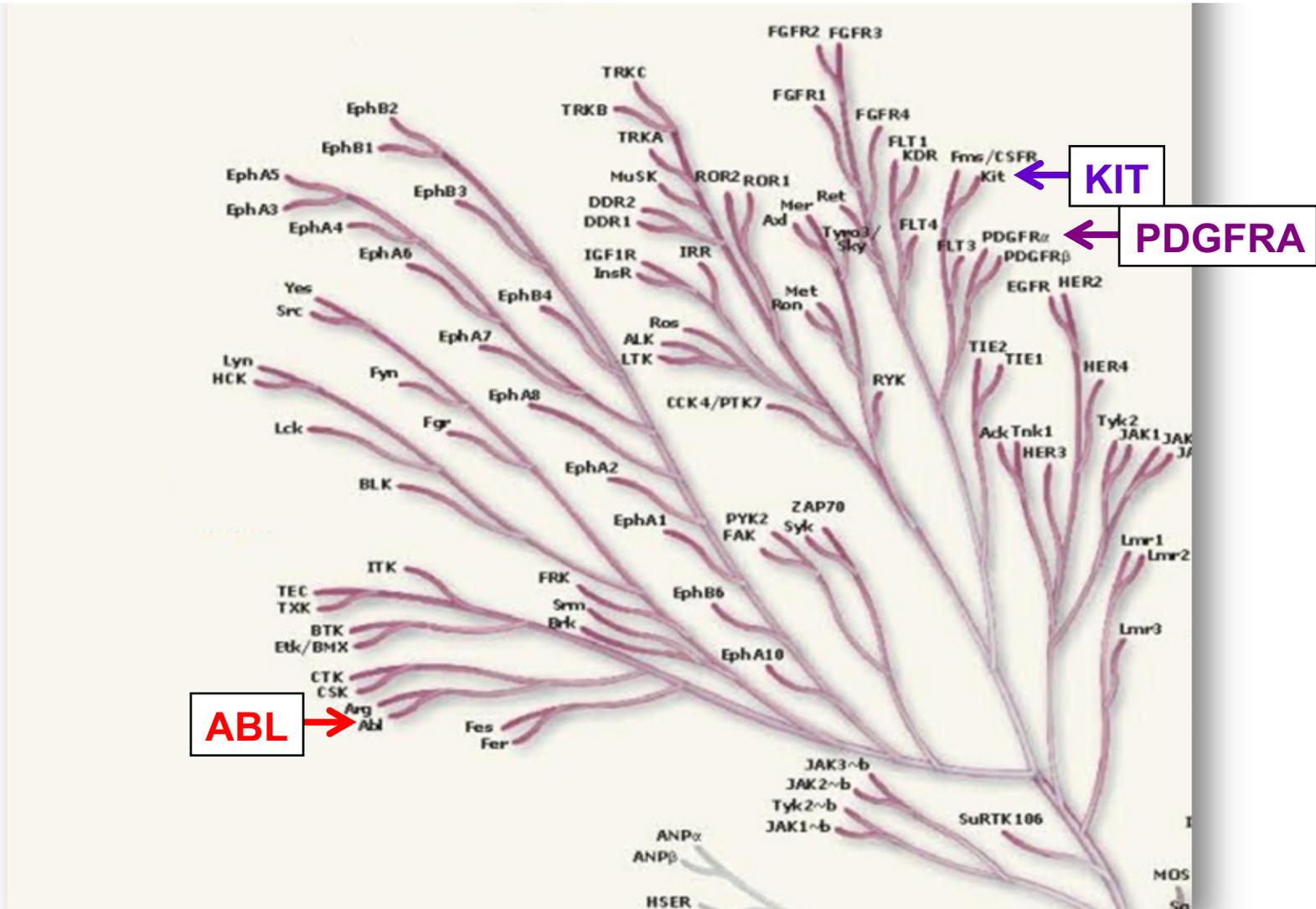
**DANIEL VASELLA, M.D.**  
Chairman and CEO, Novartis

with **ROBERT SLATER**  
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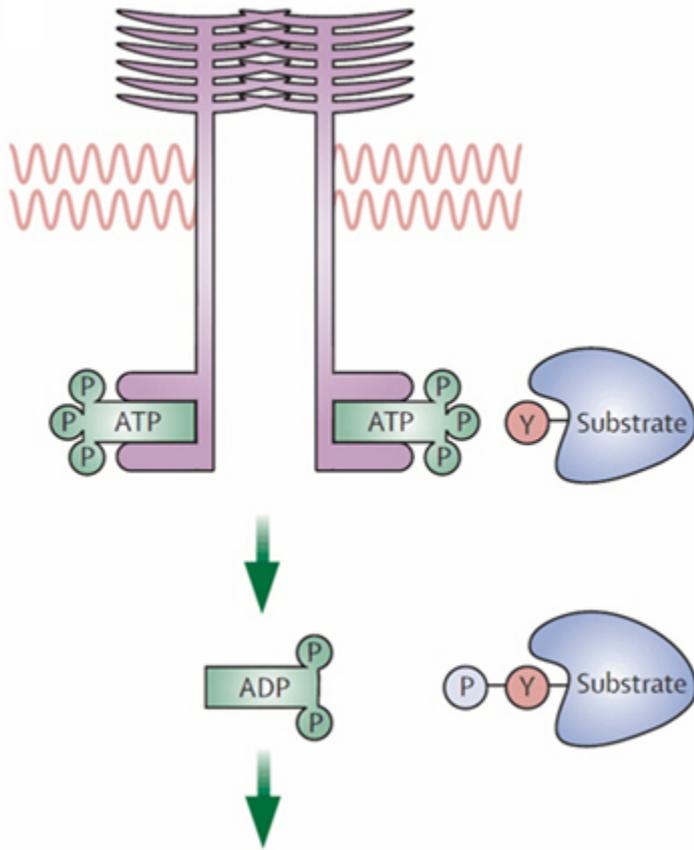
**GIST therapy has benefited from CML discoveries**

**Like BCR-ABL, KIT and PDGFR are also tyrosine kinase enzymes. Many of the drugs that are effective in CML have also proven to be effective in GIST.**

KIT and PDGFRA are close “cousins”; ABL is a distant cousin.

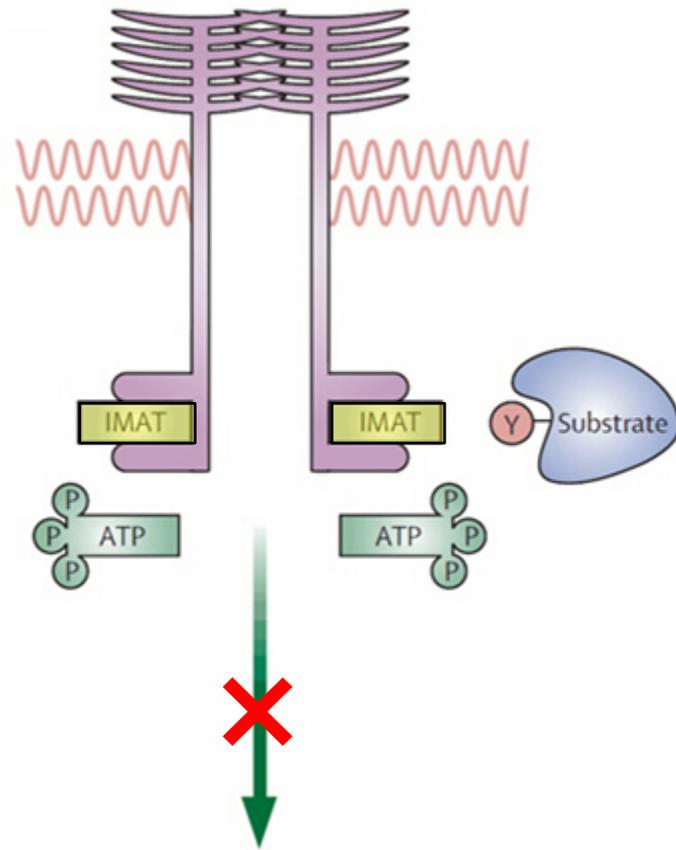


**untreated**



**KIT-activated signal transduction;  
GIST proliferation and survival**

**KIT inhibitor (e.g. imatinib)**



**inhibition of KIT;  
reduced GIST proliferation;  
apoptosis (cell death)**

Rubin et al., *Lancet* 2007

*Gleevec started the “targeted chemotherapy” wave.*

## TKI oral cancer drugs (partial list)

<u>generic and trade names</u>	<u>molecular targets</u>	<u>cancer indications</u>
imatinib (gleevec; 2001)	c-KIT, BCR-ABL	CML, GIST
erlotinib (tarceva; 2004)	EGFR	NSCLC
sorafenib (nexavar; 2005)	RAF, VEGFR	renal
dasatinib (sprycel; 2006)	c-KIT, BCR-ABL	CML, GIST
sunitinib (sutent; 2006)	PDGFR, KIT	renal, GIST
lapatinib (tykerb; 2007)	HER2	breast ca.
crizotinib (xalkori; 2011)	ALK	NSCLC
palbociclib (ibrance, 2015)	CDK4	breast ca.

## The need for additional drugs for GIST:

- Some GISTs are imatinib-resistant from the outset; e.g., the most common PDGFRA mutation in GIST (D842V) is resistant to both imatinib and sunitinib.
- For some individuals, imatinib side effects are severe and compromise effective treatment.
- Imatinib halts the growth of most GISTs, but does not eliminate them; over time, GIST tumours tend to become imatinib-resistant, due to additional mutations arising.

**Drugs approved for use in GIST:**  
**the “big three” TKIs**

**First-line: Imatinib (Gleevec - Novartis; 2001)**

**Second-line: Sunitinib (Sutent - Pfizer; 2006)**

**Third-line: Regorafenib (Stivarga - Bayer; 2013)**

## New drugs currently being tested in GIST clinical trials

### *Tyrosine kinase inhibitors*

pazopanib; ponatinib; XL820

### *HSP90 (“heat shock protein 90”) inhibitors*

STA-9090; AT13387; AUY922

### *Drugs being tested in combination with imatinib*

BYL719I; BKM120; perifosine

Serrano and George, Recent advances in the treatment of GIST, *Ther. Adv. Med. Oncol.* 6: 115-127, 2014; Bauer and Joensuu, Emerging agents for the treatment of advanced, imatinib-resistant gastrointestinal stromal tumors: current status and future directions, *Drugs* 75:1323-34, 2015.

**Table 1** Experimental agents studied in advanced gastrointestinal stromal tumors (GIST)

Drug	Key molecular targets	Manufacturer	Setting tested	Phase	Common dose	Frequent adverse effects
Nilotinib (Tasigna <sup>®</sup> )	KIT, PDGFRs, BCR-ABL	Novartis	First line, third line	III	400 mg bid	Nausea/vomiting, fatigue, skin rash
Masitinib (Masivet <sup>®</sup> )	KIT, PDGFR, FGFR3, Lyn, FAK	AB science	First line, second line	II, III, ongoing	First line, 7.5 mg/kg; second line, 125 mg/kg	Mild asthenia, diarrhea, nausea, edema, muscle spasms, rash, neutropenia
Sorafenib (Nexavar <sup>®</sup> )	KIT, VEGFRs, PDGFR, RAF	Bayer	≥Third line	Retro-spective cohorts	400 mg bid	Rash, hand-foot syndrome, diarrhea, hypertension
Dovitinib	KIT, PDGFR, VEGFR 1-3, FGFRs 1-3, FLT3	Novartis	Second line, third line	II	500 mg od (5 days on/2 days off)	Hypertension, fatigue, vomiting, asthenia, neutropenia, thrombocytopenia, hypertriglyceridemia
Pazopanib (Votrient <sup>®</sup> )	KIT, PDGFR $\alpha$ , VEGFR 1-3	GlaxoSmithKline	Second line, third line, >third line	II	800 mg od	Diarrhea, fatigue, elevated serum liver enzyme levels, mild hand-foot-syndrome.
Ponatinib (Iclusig <sup>®</sup> )	BCR-ABL, KIT (including exon 17 mutants)	Ariad	Third line, second line	II	45 mg od	Rash, fatigue, myalgia, dry skin, headache, abdominal pain, constipation, arterial thrombosis
Cabozantinib (Cometriq <sup>®</sup> )	RET, MET, VEGFR 1-3, KIT, TRK $\beta$ , FLT-3, AXL, TIE-2	Exelixis	Second line	II	140 mg od	Fatigue, diarrhea, nausea, weight loss, hypertension, hand-foot syndrome, taste alterations
Vandetanib (Caprelsa <sup>®</sup> )	VEGFRs, EGFR, RET	Novartis	Any line, ongoing	II	300 mg od	Diarrhea, hypertension, acne, asthenia, QTc prolongation, rash
Famitinib	KIT, PDGFRs, VEGFR 2 and 3, RET FLT1, FLT3	Jiangsu Hengrui Medicine	Second line	II	25 mg od	Hypertension, hand-foot syndrome, mucositis, fatigue, neuropathy
Vatalanib	KIT, VEGFR, PDGFR	Bayer Schering, Novartis	Second line	II	1250 mg od	Dizziness, nausea, hypertension
Dasatinib (Sprycel <sup>®</sup> )	KIT, PDGFRs, BCR-ABL, SRC	Bristol-Myers Squibb	First line ≥ third line	II	100 mg od	Fluid retention, pleural effusion, diarrhea
BLU285	KIT D816V, PDGFR D842 -mutants	Blueprint Medicines	–		NA	NA
Crenolanib	PDGFRA (including D842), FLT3	AROG	All lines	II	NA	Nausea, vomiting, serum liver transaminase level elevation
Ganetespib (STA-9090)	HSP90	Synta	≥First line	II	200 mg/m <sup>2</sup> iv weekly (3 weeks on, 1 week off)	Diarrhea, fatigue, nausea, vomiting, increased alkaline phosphatase, headache, insomnia, abdominal pain
BIIB021	HSP90	Biogen Idec	Third line	II	600 mg po twice weekly, or 400 mg thrice weekly	Dizziness, syncope, elevation of alkaline phosphatase

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