

GIST 101: An Introduction to the Biology and Medicine of GIST

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Disclaimer:

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

LifeFest, Miami, July 2018

- What is GIST? What causes it?
- How are GISTs diagnosed and treated?
- What are the KIT and PDGFRA genes/ proteins?
- How do “TKI” drugs (such as Gleevec) work?
- What new drugs are now in clinical trials?

Green notes are references to upcoming presentations at LifeFest 2018.

GIST “Top Ten List” for new patients



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GIST Top Ten List for New Patients

Prepared by David Josephy (President, LRG Canada) and Ginger Sawyer (GIST Support International)

1. Gastrointestinal stromal tumors (GISTs) are uncommon tumors of the digestive (gastrointestinal; GI) tract. More than half of GISTs start in the muscular wall of the stomach; most others are in the small intestine; rarely, GISTs are found at other GI sites. GISTs aren't the same as other, more common GI tract cancers. GISTs are very treatable.
2. GIST strikes randomly. When GIST patients gather, they are often surprised at the diversity of people in the room – male or female, young or old, rich or poor, of European or Asian or African heritage. We don't know of any “lifestyle” factors, such as diet, place of residence, occupation, or chemical exposures that cause GIST. In short – getting GIST was not your fault and you should not feel any shame or guilt about having the condition.
3. GISTs are rare! Many doctors have never seen a patient who has GIST. You should definitely be treated by an oncologist (cancer specialist). If possible, find a GIST specialist at a major cancer center.
4. When you are first diagnosed with GIST, ask for a copy of your pathology report. This information will help you when you discuss your prognosis and treatment with your doctors. In most

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-  English
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Nous sommes en processus de faire les reparations pour que se site soit bilingue. Certaines pages n'ont pas encore été traduites en français. Merci pour votre compréhension et patience durant ce temps. Nous sommes desoler pour l'inconvenience.

What is GIST (Gastro-Intestinal Stromal Tumour)?

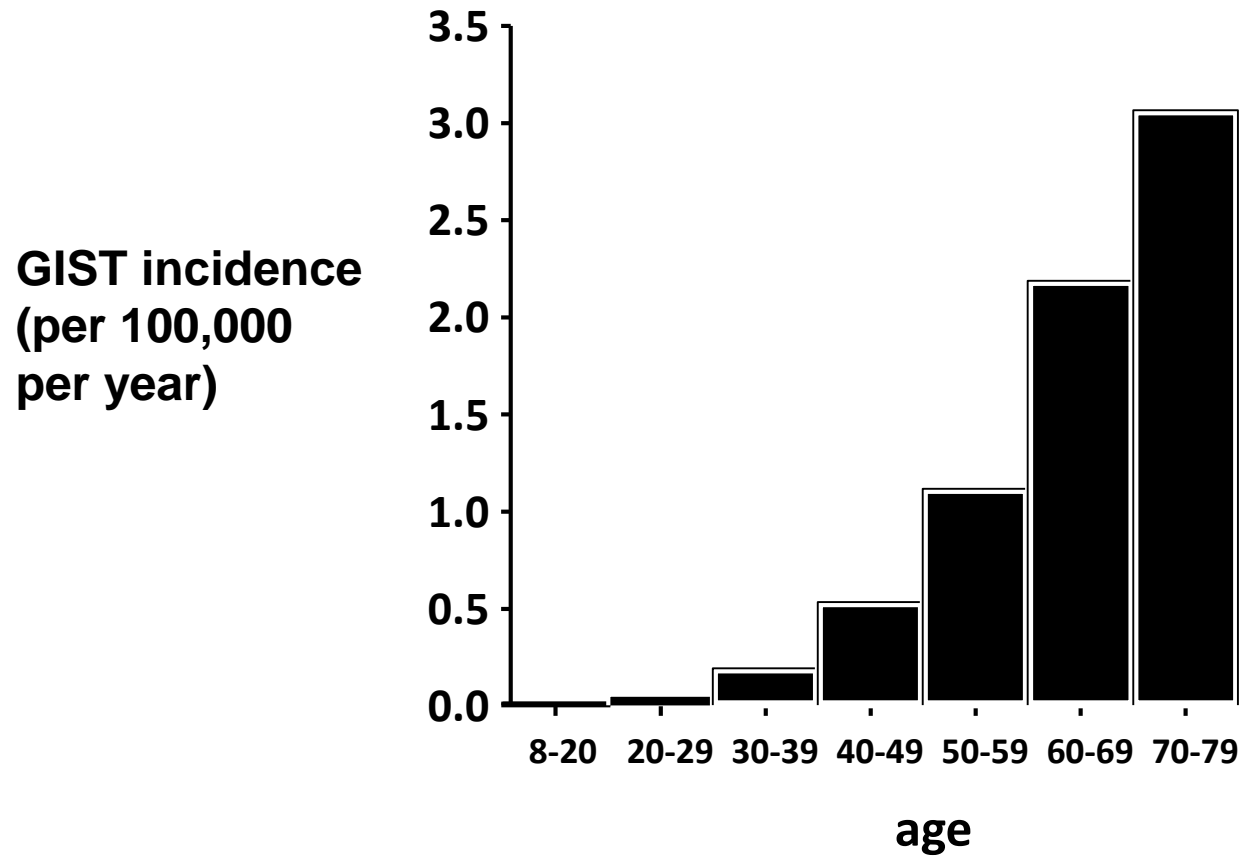
- **an uncommon cancer; about 5,000 new cases per year in the USA**
- **poorly understood until 1998; rapid progress has been made since then**

What causes GIST?

GIST can be inherited (“running in the family”), but this is *exceedingly rare*; almost all GISTs are “sporadic” (not familial).

No environmental, occupational, dietary, or lifestyle 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 for most cancers.

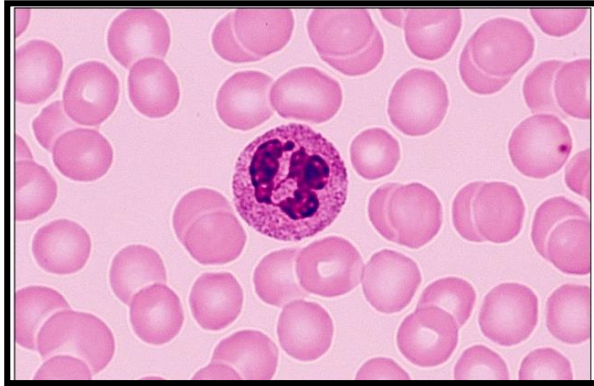


**GIST is a sarcoma. But, what is a sarcoma?
How does a sarcoma differ from other types of cancer?**

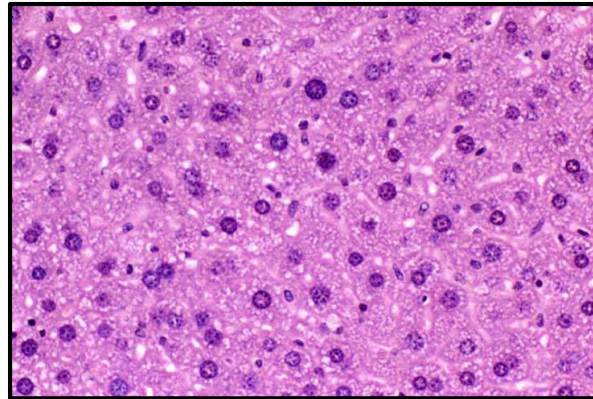
Cells, tissues, organs, and cancers

There are at least 200 types of cells in the human body.

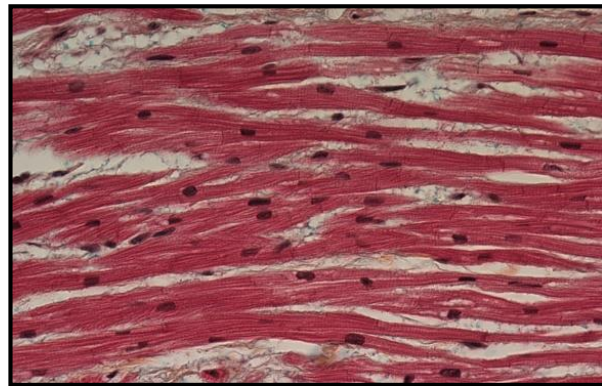
Even a single organ, such as the lung, is formed from many types of cells.



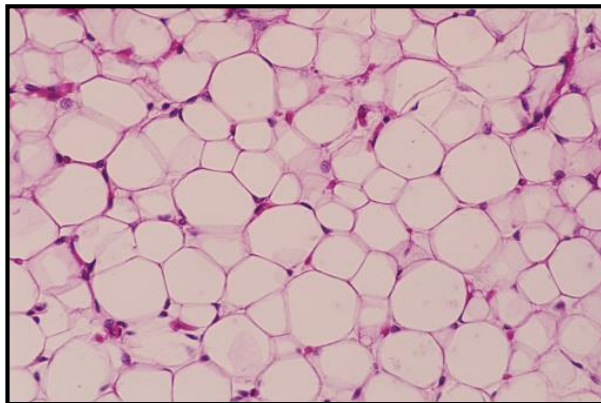
red and white blood cells



hepatocytes (liver)



cardiomyocytes (heart)

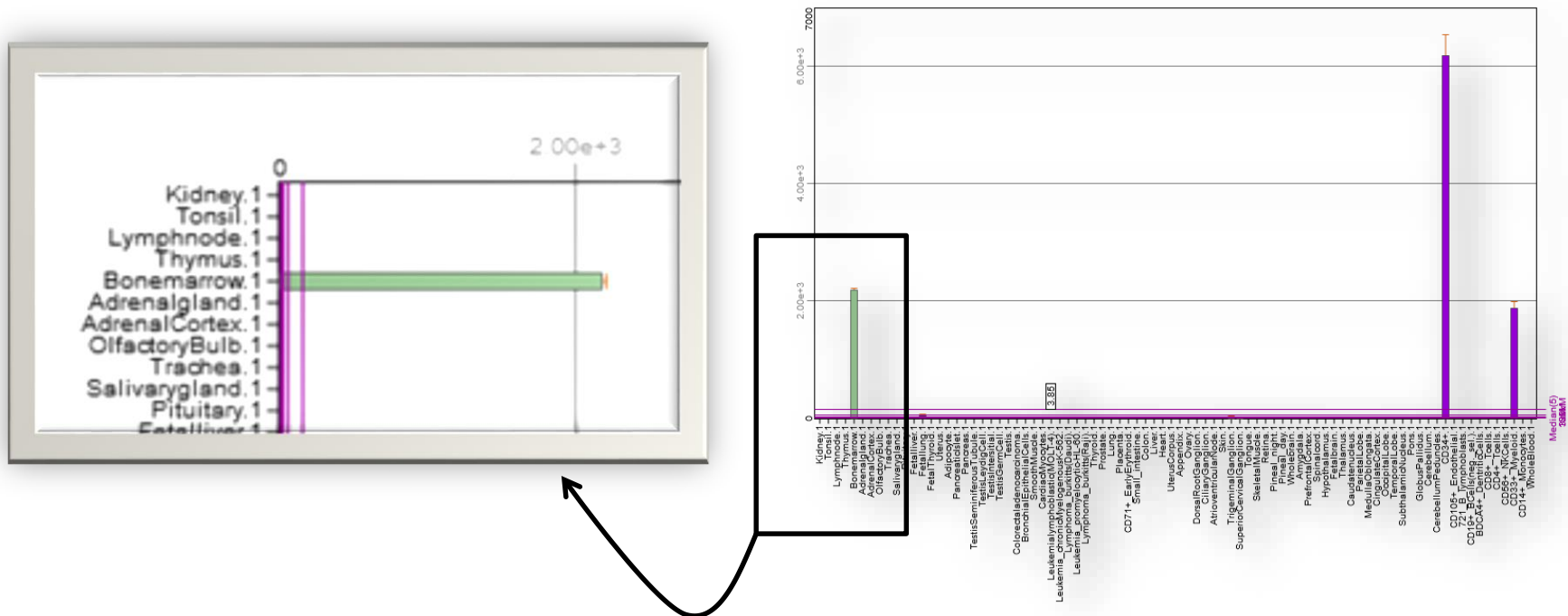


adipocytes (fat tissue)

What makes one cell type different from another?

Mainly: The production (“expression”) of specific proteins.

Here’s an example: The enzyme “myeloperoxidase” is produced only in the bone marrow and a few types of white blood cells.



*Specific tumours also show distinctive protein-expression patterns.
Analysis of protein expression is very important for cancer pathology.*

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 - and its treatment.

Identifying the cell type (usually, by examining a surgical specimen) is the important task of the pathologist.

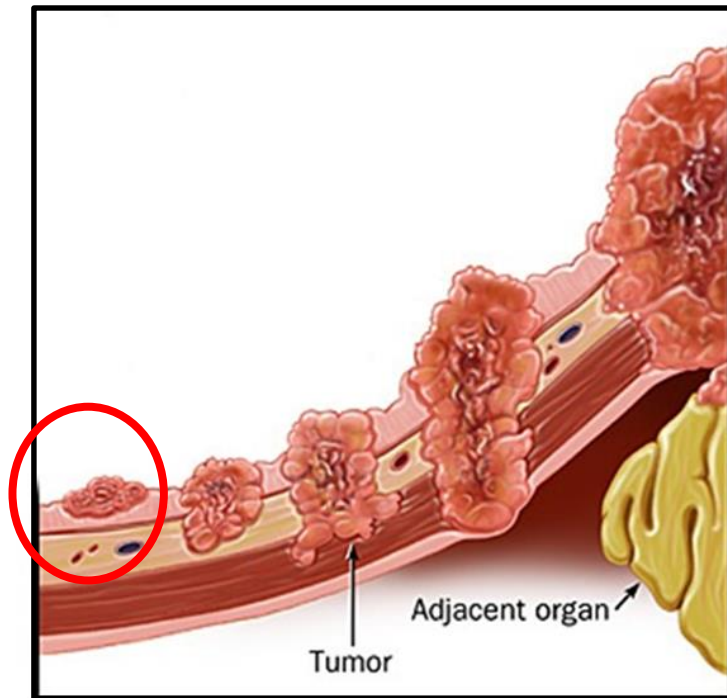
Carcinomas and sarcomas: two different classes of cancers, arising in two different types of tissues.

Most cancers (skin, colon, lung, bladder, prostate, breast, etc.) are *carcinomas*, which arise in epithelial (“lining”) cells.

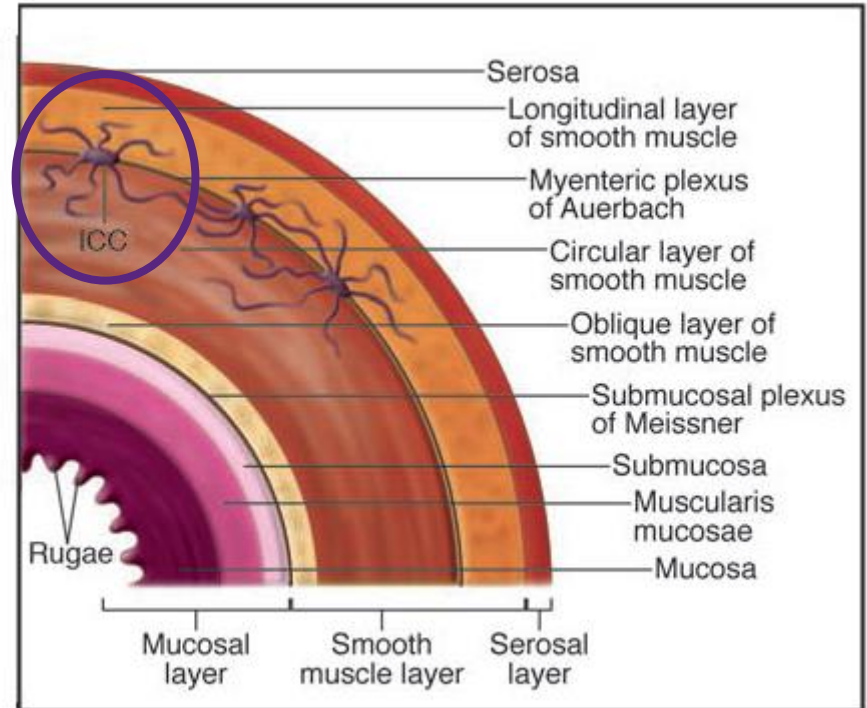
GIST is not a carcinoma; it is a *sarcoma*.

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

Carcinomas start on the *inside* of the g.i. tract (in the epithelial lining).



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



Coffey *et al.*, *J. Clin. Invest.* 117: 70-80, 2007.

GIST is a type of “soft-tissue sarcoma” (STS).

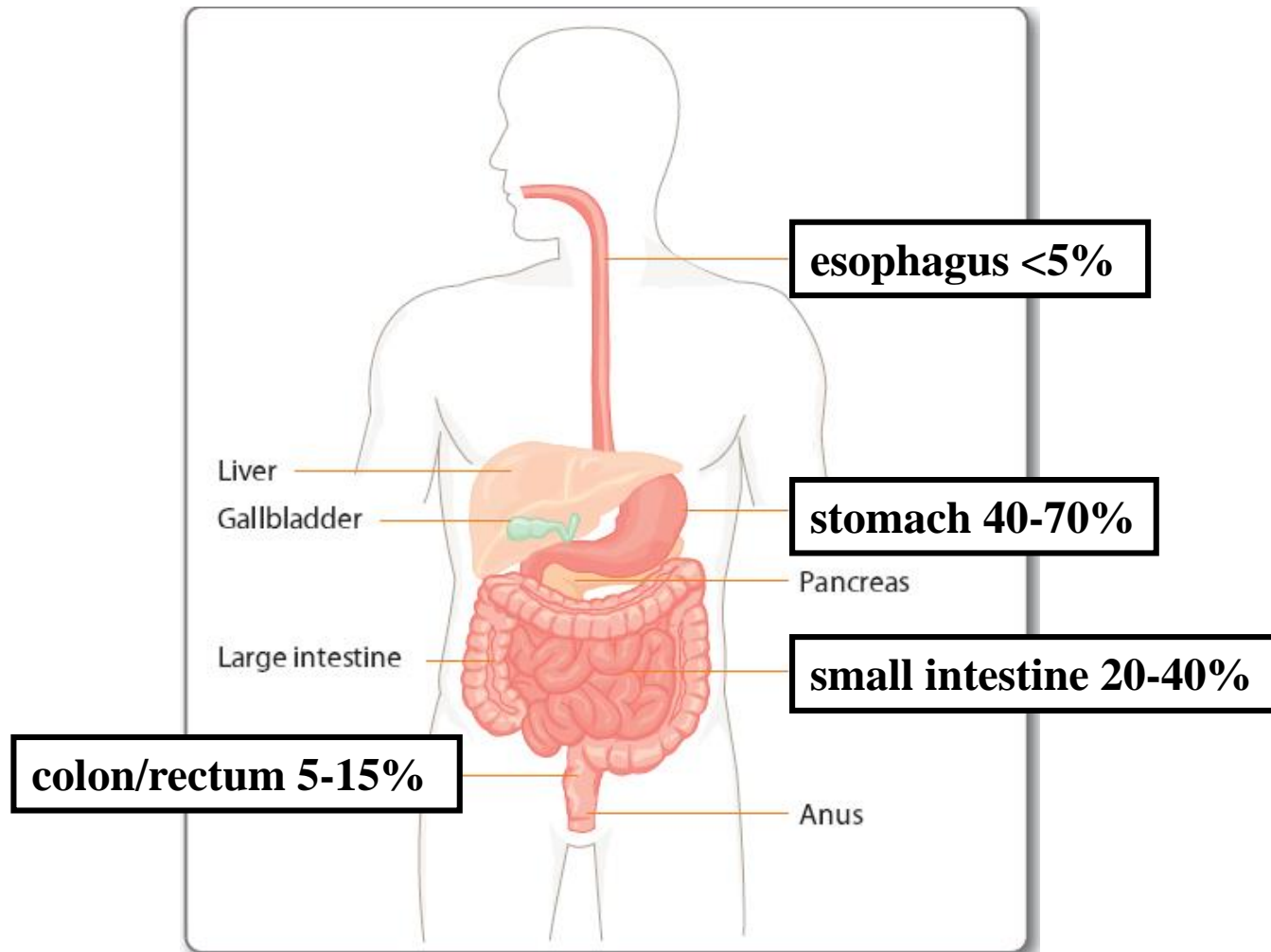
(Sarcomas can also occur in bones, which are *not* soft!)

There are many types of STS: fibrosarcoma, liposarcoma, leiomyosarcoma, etc.

However, GIST is different from other STS:

- better understood at the molecular level;**
- treated with a different set of drugs;**
- usually, much better outcomes.**

All GISTs arise in the same cell type (ICC - *see later slide*), regardless of their location along the GI tract.



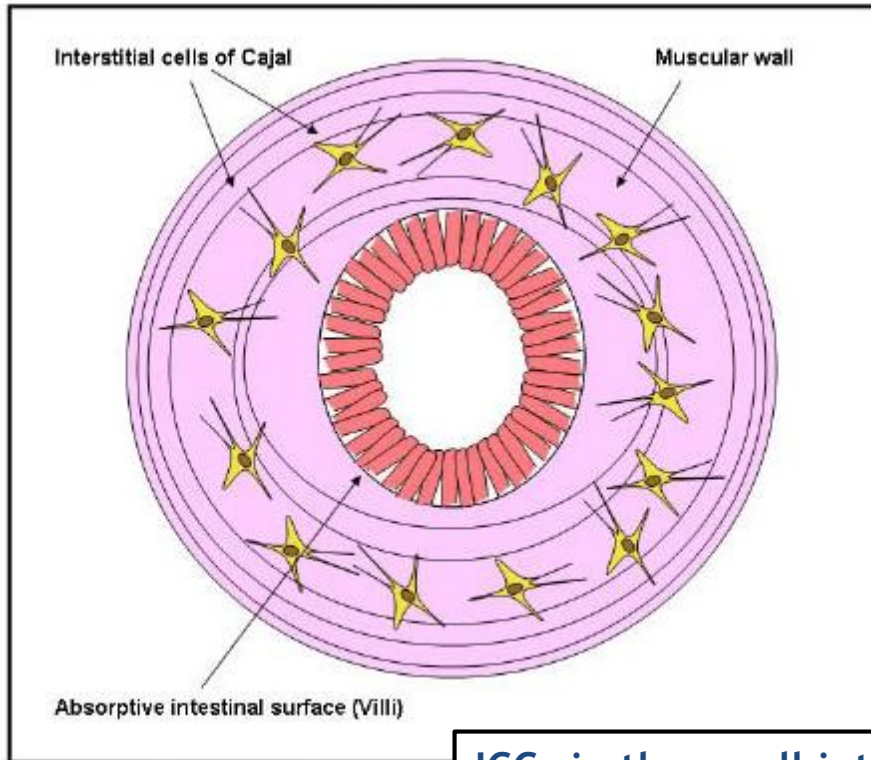
A GIST that starts in the stomach is a GIST

(... 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).

ICCs: The “interstitial cells of Cajal”: the cells where GISTs start



ICCs in the small intestine

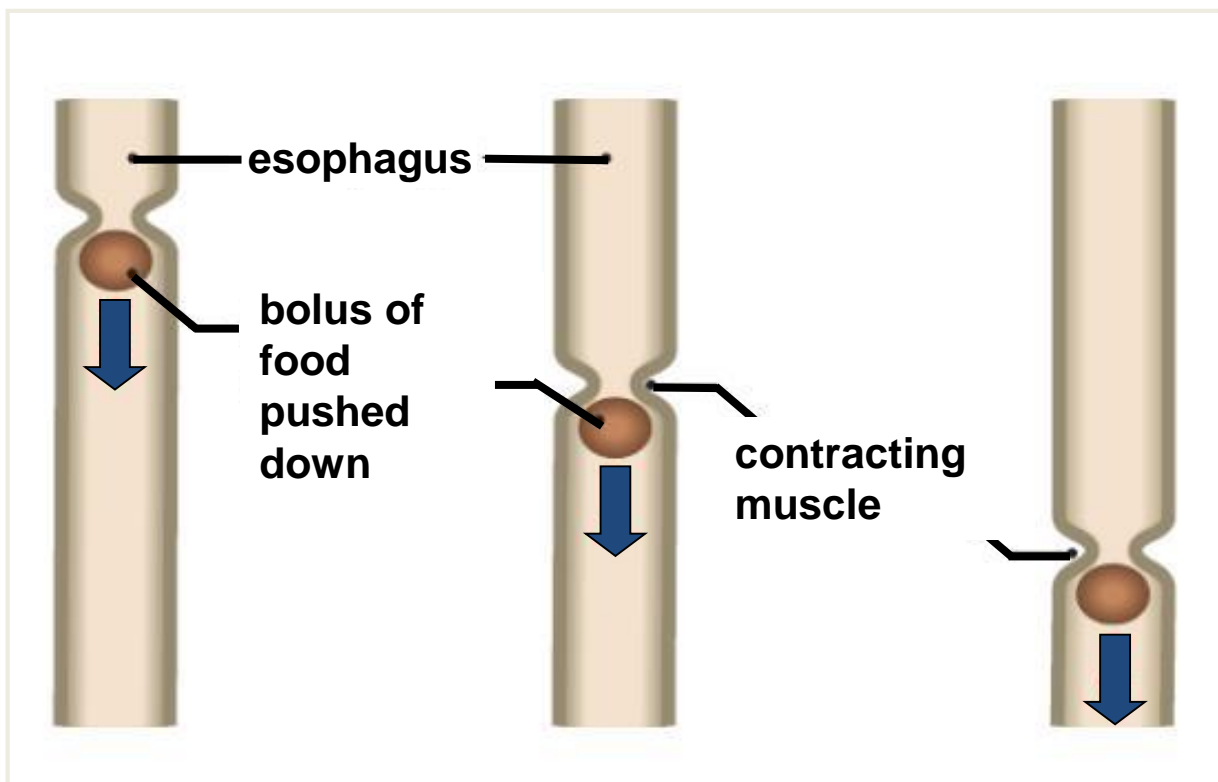


Santiago Ramón y Cajal
(1852-1934)

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

What are ICCs?

ICC's are the neuronal “pacemaker” cells that coordinate peristalsis: the regular waves of muscle action that push food along the g.i. tract. ICC's mediate communication between the autonomic nervous system and the g.i. smooth muscle: they send out the electrical signals that stimulate the smooth muscle to contract.



ICCs and GIST

Since about 1998, it has become clear that GISTs develop from ICCs (or perhaps from a closely-related precursor to ICCs).

- **GISTs develop only where ICCs reside, along the g.i. tract**
- **GISTs and ICCs express very similar sets of proteins, including KIT - a distinctive pattern of expression that is not seen in any other cell type.**

GISTs are cancers; there are probably no truly “benign” GISTs.

Like other cancers, GISTs are 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.

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

GIST Diagnosis

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

A story that we hear far too often:

“The patient is a man in his 60s ... 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.

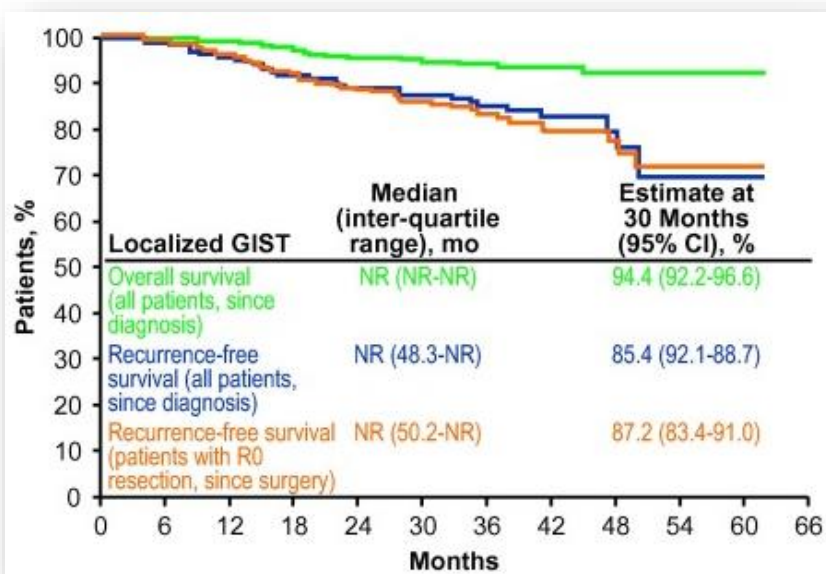
However, the primary GIST can metastasize – *i.e.*, spread to new sites, especially to the liver and the peritoneum (the membrane lining the abdominal cavity); rarely to the bone, lung, etc.

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

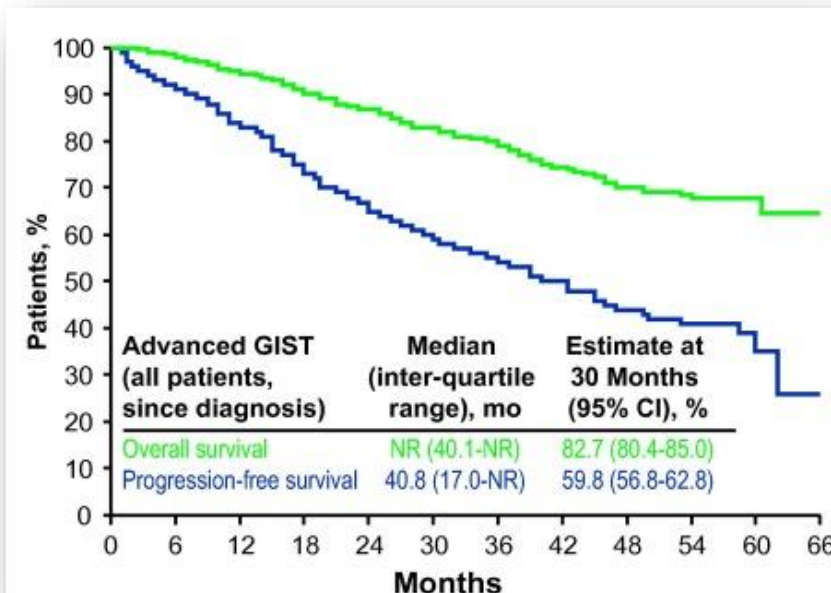
Once a GIST has metastasized, surgery alone cannot be curative: systemic therapy (usually, drug therapy) is required.

GIST Prognosis

Patients are living with GIST for many years, and treatment outcomes are continuing to improve.



Localized GIST



Advanced GIST

Barrios ... Reichardt, *Eur. J. Cancer* 51: 2423-2433, 2015.

Localized GIST: Risk Assessment

→ Dr. Miettinen, Saturday 10:45 a.m.

The risk that a localized GIST will subsequently metastasize can be estimated, based on factors including ...

Size of the tumour 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!

Location of the primary tumour (stomach vs small intestine vs colon ...)

Mutational type (to be discussed later in this presentation)

These assessments are statistical predictions only – like estimating the probability that it will rain next week.

Localized GIST: Adjuvant therapy

“Adjuvant” therapy: taking imatinib after surgical removal of a localized GIST, to reduce the risk of recurrence or metastasis.

The medical consensus regarding adjuvant therapy continues to evolve; a three-year course is now typical. Adjuvant treatment is much more likely to be prescribed for a high-risk GIST.

Localized GIST: Adjuvant therapy

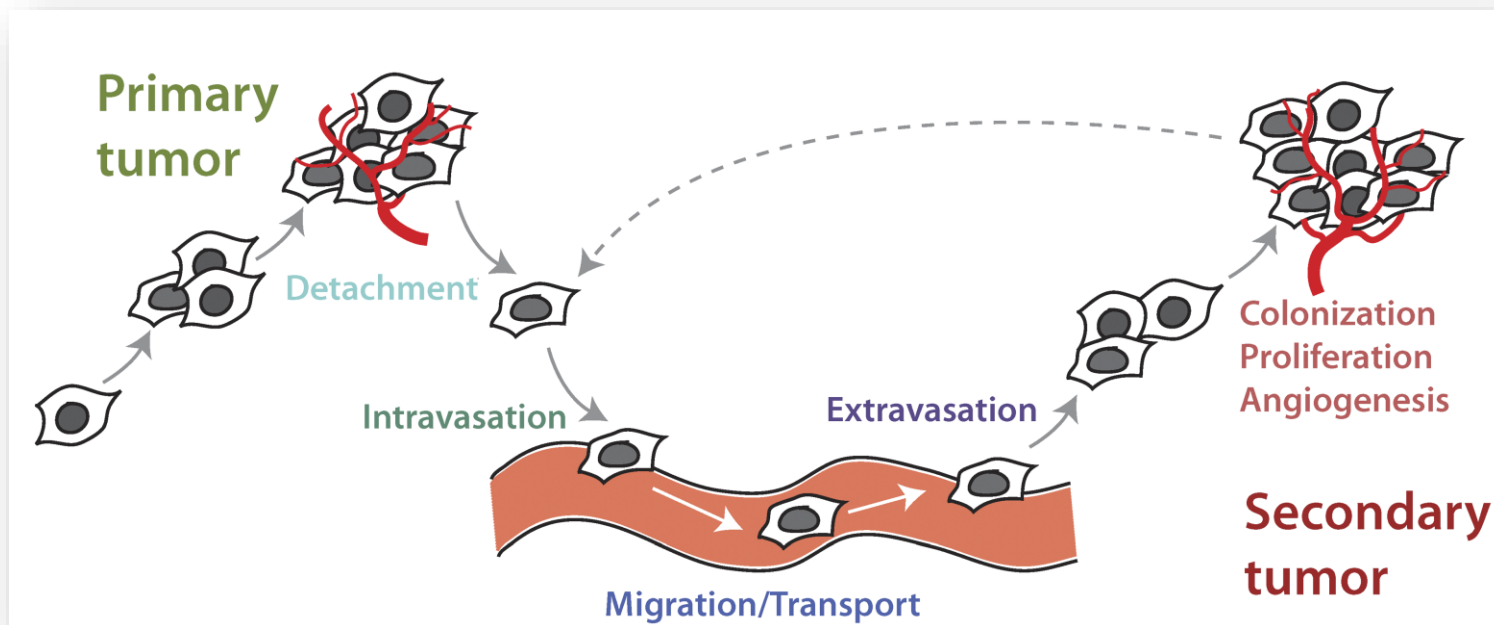
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Metastases (“mets”), wherever they grow, have the biological properties of the primary tumor, because they are descendants of the same cells.

(I am still a Canadian, even though I am currently in Miami!)

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



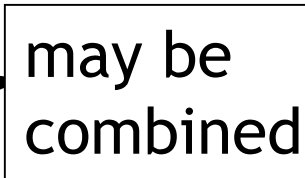
Treatment of metastatic GIST:

→ Dr. Trent and Dr. Heinrich, Saturday 9 a.m.

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 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): 2nd line
 - ❖ Stivarga (regorafenib): 3rd line
 - ❖ Clinical trials
- 
- may be combined

Possible new approaches for treatment of metastatic GIST (as yet unproven)

→ **Clinical Panel of Experts, Saturday 10:45 a.m.**

Immunotherapy:

Tan *et al.*, Current status of immunotherapy for GIST, *Cancer Gene Ther.* 24: 130-133, 2017.

Monoclonal antibodies:

Wagner *et al.*, A phase II study of a human anti-PDGFR α monoclonal antibody (olaratumab, IMC-3G3) in previously treated patients with metastatic GIST, *Ann. Oncol.* 28: 541-546, 2017.

Radiotherapy:

Gatto *et al.*, Radiotherapy in the management of GIST: state of the art and new potential scenarios, *Clin. Sarcoma Res.* 7, 2017.

The Molecular Biology of GIST

Fundamental discoveries in molecular genetics (made esp. since 1998) have revolutionized our understanding of GIST biology and treatment.

GIST and the KIT protein

Almost all GIST tumours express a specific protein called “KIT”; most GISTs are “driven” by mutations in the gene that encodes KIT.

Gain-of-Function Mutations of *c-kit* in Human Gastrointestinal Stromal Tumors

Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshiro Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiro Kitamura†

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the human digestive tract, but their molecular etiology and cellular origin are unknown. Sequencing of *c-kit* complementary DNA, which encodes a proto-oncogenic receptor tyrosine kinase (KIT), from five GISTs revealed mutations in the region between the transmembrane and tyrosine kinase domains. All of the corresponding mutant KIT proteins were constitutively activated without the KIT ligand, stem cell factor (SCF). Stable transfection of the mutant *c-kit* complementary DNAs induced malignant transformation of Ba/F3 murine lymphoid cells, suggesting that the mutations contribute to tumor development. GISTs may originate from the interstitial cells of Cajal (ICCs) because the development of ICCs is dependent on the SCF-KIT interaction and because, like GISTs, these cells express both KIT and CD34.

The *c-kit* proto-oncogene encodes a type III receptor tyrosine kinase (KIT) (1), the ligand of which is SCF (2). SCF-KIT interaction is essential for development of melanocytes, erythrocytes, germ cells, mast cells and ICCs (3, 4). Gain-of-function mutations of the *c-kit* gene have been found in several tumor mast cell lines of rodents and humans (5, 6) and in mast cell tumors of humans (7). Here we investigate the mutational status of *c-kit* in mesenchymal tumors of the human gastrointestinal (GI) tract.

SCIENCE • VOL. 279 • 23 JANUARY 1998

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Yukihiro Kitamura, M.D.



Seiichi Hirota, M.D.

Osaka University Medical School

1998: The breakthrough discovery

Mutations that “drive” GIST

1998: In most GISTs, a **mutation in the *KIT* gene (DNA)** causes the cells to express an **activated** form of KIT protein that forces the cells to keep dividing.

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

“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 “wildtype”. 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 of GISTS.

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

→ Dr. Helman, Saturday 8:05 a.m.

→ Dr. Gottlieb, Saturday 3:30 p.m.

“Wildtype” GIST

Mutations in several other genes have subsequently been implicated in some wildtype GISTs: B-RAF, NF1, K-RAS, NTRK ... the list continues to grow.

GIST: several related diseases, not just one.

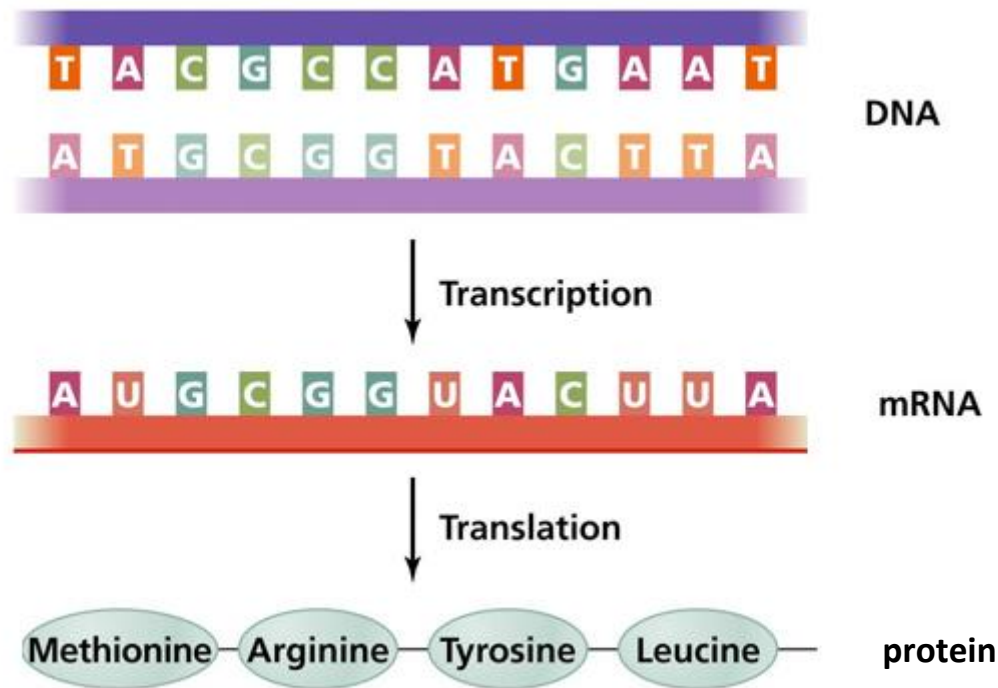
As research progresses, we are learning that GIST is really a constellation of several related diseases (perhaps ten or even more) with different molecular and clinical characteristics.

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

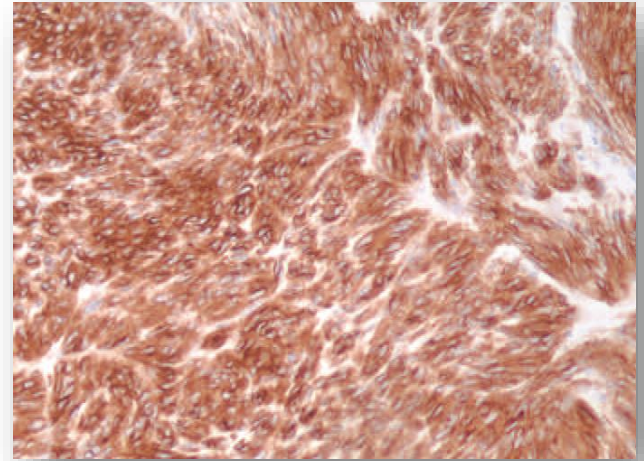
Genes (DNA) are the code (blueprints) for construction of the cell's proteins. The human genome encodes about 20,000 different kinds of proteins.



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. The stained tissue is examined under the microscope.**



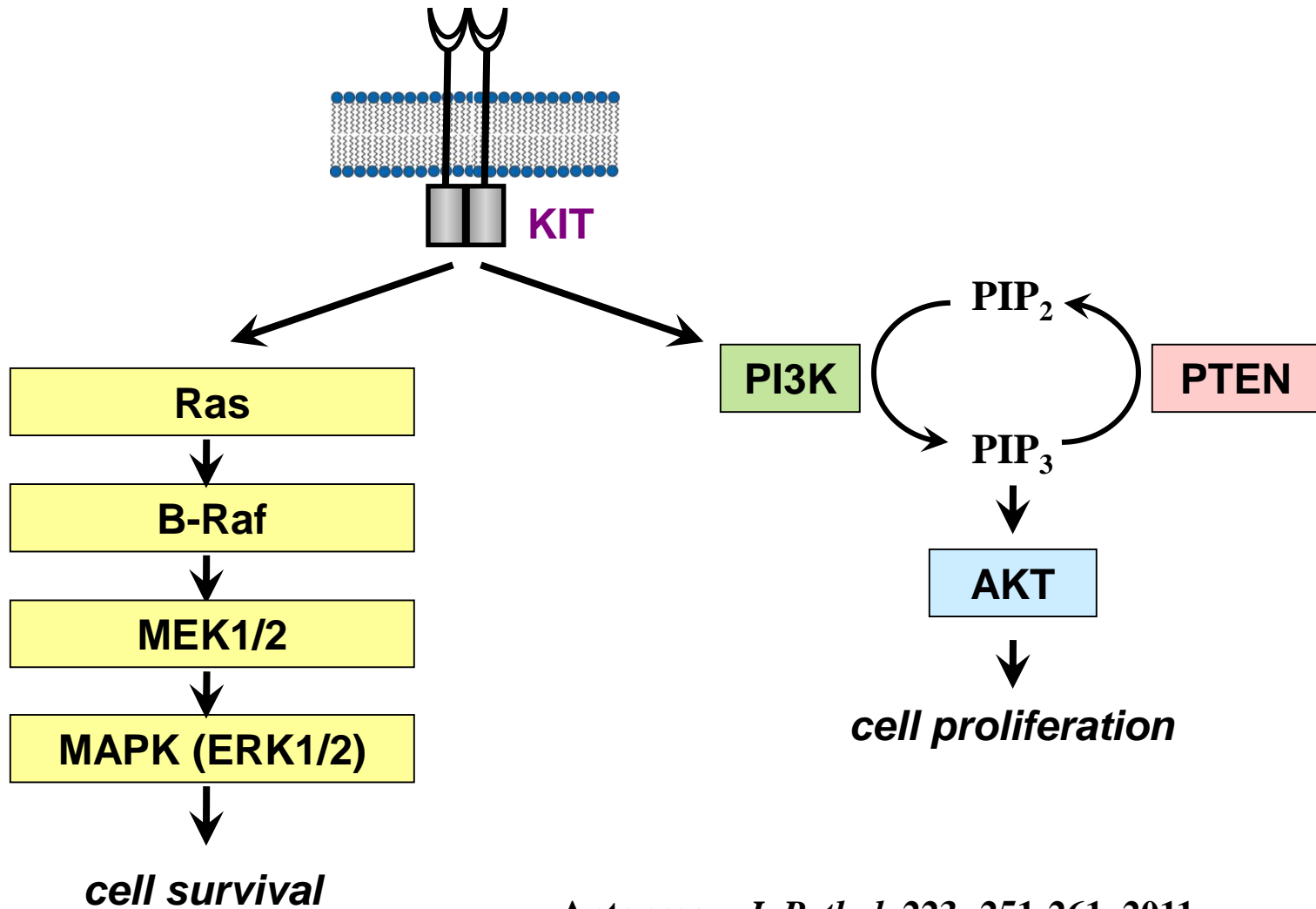
Turner and Goldsmith, *Arch. Pathol. Lab. Med.* 133: 1370-1374, 2009.

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 and thereby modulates their activities (“signal transduction cascade”).

KIT signaling pathways in GIST



Antonescu, *J. Pathol.* 223: 251-261, 2011;
Patel, *Curr. Oncol. Rep.* 15: 386-395, 2013.

In normal ICCs:

A “growth factor” binds to KIT (“steps on the gas pedal”). In response, KIT becomes active and instructs the cell to grow and divide.

In GIST cells:

The *KIT* gene is mutated.

An altered form of KIT protein is produced.

This altered KIT protein is “always turned on” (“stuck gas pedal”), even in the absence of the growth factor. The 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 654th 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 during cells division in development or adulthood, but not affecting germ cells (egg or sperm cells)
- the somatic 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:

- several different genes**
- several different sites within the *KIT* gene, affecting different regions 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).

“There are only two reasons for a doctor *not* to perform mutational testing on a GIST:

**He doesn't have the paraffin block, or
he doesn't have an envelope and a stamp.”**

Dr Peter Reichardt, Sitges, Spain, May 2016.

→ Dr. Rosenberg, Saturday 1:30 p.m.

Like bombs during the Blitz, mutations strike the KIT gene randomly - but the consequences depend on exactly where the bomb hits.



Some GISTs (10-15%) are driven by mutations in a different gene, *PDGFRA*, which is a “cousin” of *KIT*.

PDGFRA = Platelet-Derived Growth Factor Receptor- α

These GISTs arise almost exclusively in the stomach.

KIT and *PDGFRA* mutations in GIST are mutually exclusive.

A common mutation in *PDGFRA* is the “notoriously imatinib-resistant” D842V.

Medical management of advanced (metastatic) GIST: “targeted” drug therapy for GIST

Before the discovery of the KIT-GIST connection, the only drugs used for GIST were “cytotoxic” drugs, such as doxorubicin: little effectiveness; bad side effects.

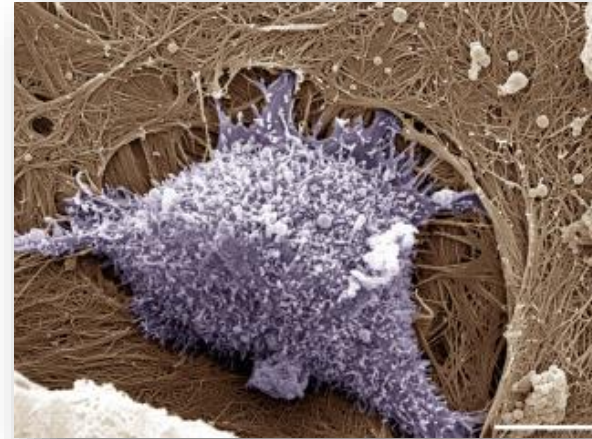
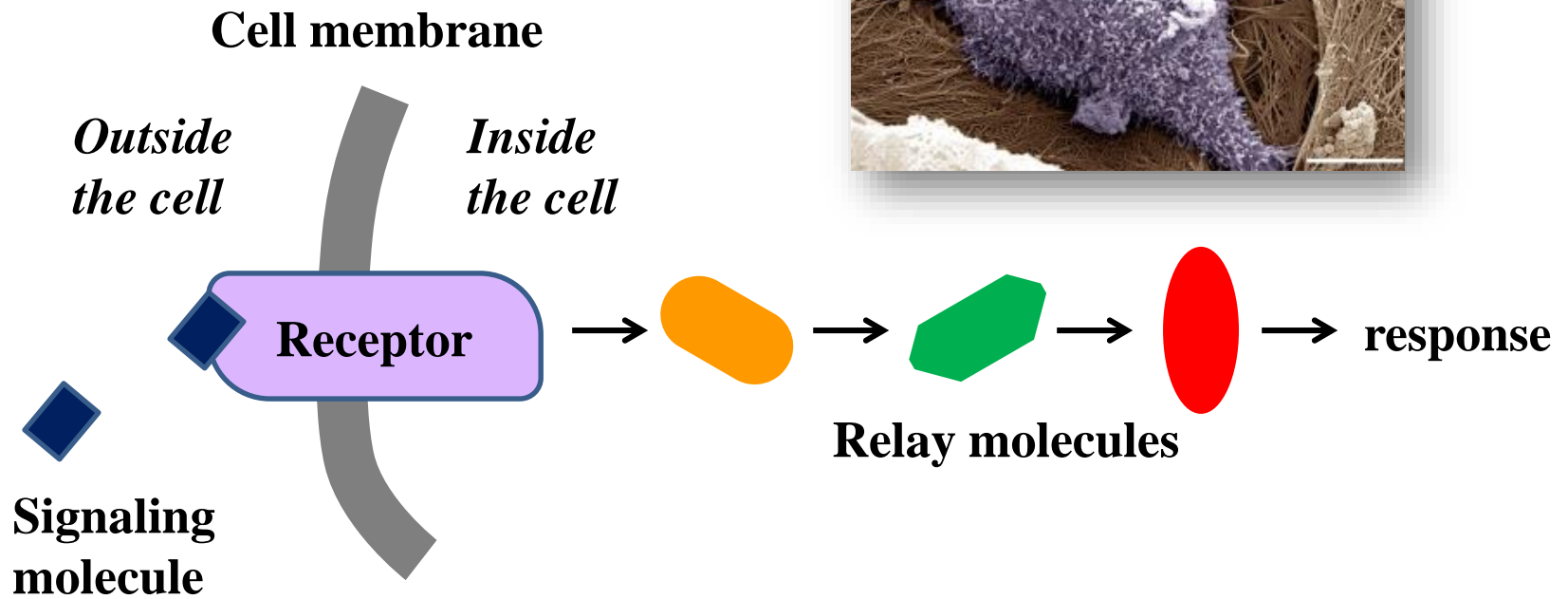
The KIT-GIST discovery started a new era in GIST therapy, post-2000, with the introduction of “targeted” drugs, starting with imatinib (Gleevec): much more effective and generally much better tolerated.

These new drugs are “tyrosine kinase inhibitors” (a.k.a. “signal transduction inhibitors”).

What are Tyrosine Kinase Inhibitors?

What are Tyrosine Kinases?

Signal transduction:



What are Tyrosine Kinases?

The receptors and relay molecules that carry out signal transduction processes are enzymes – proteins that catalyze chemical reactions.

Enzymes that use ATP to phosphorylate other proteins are called “**kinases**”. When the phosphorylation occurs on the amino acid “**tyrosine**”, we call the enzyme a **tyrosine kinase**.

Many signal transduction proteins are tyrosine kinase enzymes.

Dysfunctional - mutated - tyrosine kinases drive the uncontrolled proliferation of certain types of cancer cells – including most GISTs.

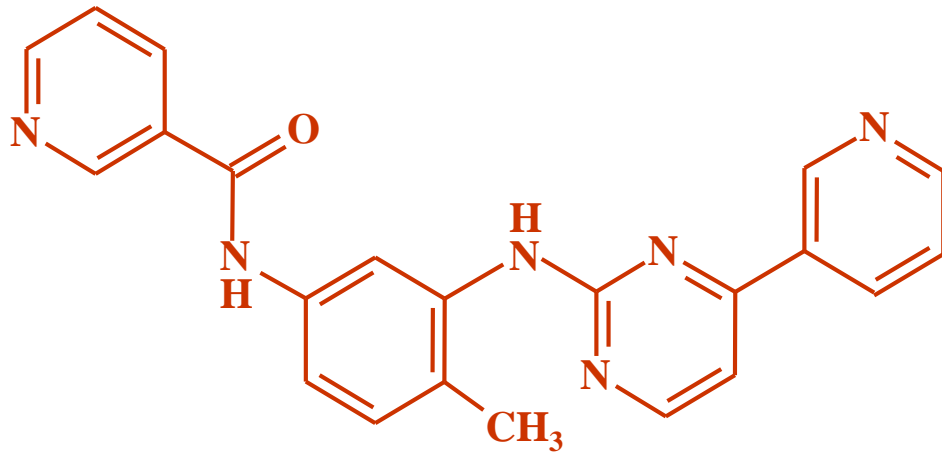
What are Tyrosine Kinases Inhibitors?

Imatinib and many other drugs are “Tyrosine Kinase Inhibitors”(TKIs): they can turn off tyrosine kinases and stop the proliferation of cancer cells.

These drugs are “small molecules”: compounds synthesized by chemists, in the lab; they are not “biologicals” (e.g., antibodies, vaccines), which are produced by cells.


***They are “orally bioavailable”:* can be taken as pills, at home.**

Gleevec (imatinib) inhibits several TKs, including KIT



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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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Gleevec started the “targeted chemotherapy” wave.

TKI oral cancer drugs (partial list)

generic and trade names

imatinib (gleevec; 2001)

erlotinib (tarceva; 2004)

sorafenib (nexavar; 2005)

dasatinib (sprycel; 2006)

sunitinib (sutent; 2006)

lapatinib (tykerb; 2007)

crizotinib (xalkori; 2011)

palbociclib (ibrance, 2015)

molecular targets

c-KIT, BCR-ABL

EGFR

RAF, VEGFR

c-KIT, BCR-ABL

PDGFR, KIT

HER2

ALK

CDK4

cancer indications

CML, GIST

NSCLC

renal

CML, GIST

renal, GIST

breast ca.

NSCLC

breast ca.

and many more to come!

Drug names: “-mabs” and “-ibs”:

The naming convention is:

- ending in “-ib”: a small-molecule TKI; usually, an oral pill.
- ending in “mab”: a “monoclonal antibody” (a protein therapeutic; *never* an oral drug; always administered i.v.); *e.g.*, ipilumimab; cetuximab; bevacizumab

The three TKIs approved for use in GIST:

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

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

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

Despite the success of these TKIs, additional GIST drugs are needed:

- 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.
- The standard drugs halt the growth of most GISTs, but do not eliminate them; over time, GIST tumours tend to **become drug-resistant (tumor progression)**, due to additional mutations arising in the metastases.

Progression: Dr. Reichardt's skeptical questions:

When I examine a GIST patient who is referred to me because he/she has experienced tumor progression while on imatinib, I first ask:

- Is it really a GIST?? (misdiagnosis?)
- Is it really a progression?? (diagnostic imaging)
- Was the patient really taking imatinib?? (compliance)

Inexperienced oncologists may abandon imatinib prematurely.

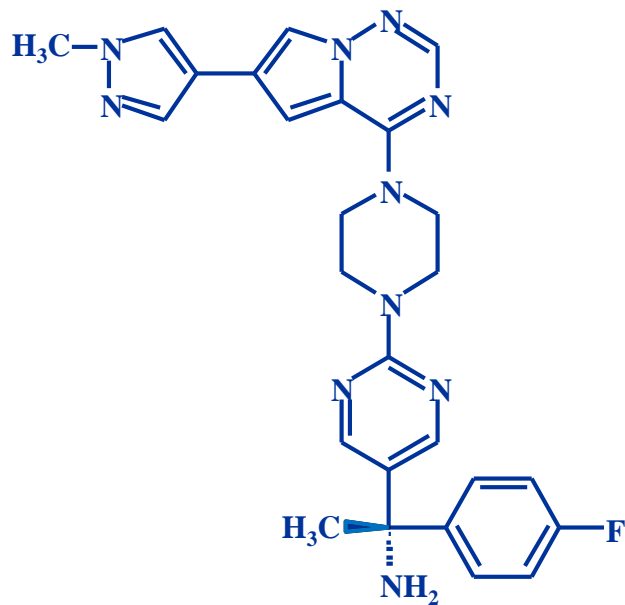
A new wave of GIST drugs is - we hope and expect - coming very soon!

None of the first-wave drugs (imatinib, sunitinib, regorafenib) was specifically developed for GIST. They were developed to treat other cancers (leukemia, kidney cancer, etc.) and later found to have activity in GIST.

Many of the new-wave drugs have been developed specifically for GIST.

→ **Pharma Panel, Saturday 9:45 a.m.**

Blueprint Medicines: BLU-285: specifically designed to inhibit KIT



avapritinib (BLU-285)

BLU-285 (avapritinib)

A precision therapy against cancers driven by KIT/PDGFR α mutations, Evans, E.K., *et al.*, *Sci. Transl. Med.* 9, eaao1690 (2017) 1 Nov. 2017

“Designed as a potent and highly selective inhibitor of KIT and PDGFR α ... mutant kinases. In contrast to [imatinib, sunitinib, and regorafenib] BLU-285 ... was able to inhibit all activation loop aberrations tested, including the difficult-to-target PDGFR α D842V and structurally homologous KIT D816V mutants.”

Ongoing clinical trials are showing that BLU-285 has very promising activity, even in heavily pretreated GIST patients.

A phase 3 randomized clinical trial comparing BLU-285 to regorafenib in 3rd-line GIST is now recruiting patients.

Imatinib resistance in GIST is often due to additional mutations that interfere with drug binding to the ATP binding site. Can we find new drugs that act by binding to a *different site on the enzyme*?

Several drug companies are developing agents based on this idea.

“Switch-pocket” inhibitors (Bai *et al.*, *Leukemia* 27: 278-285, 2013)

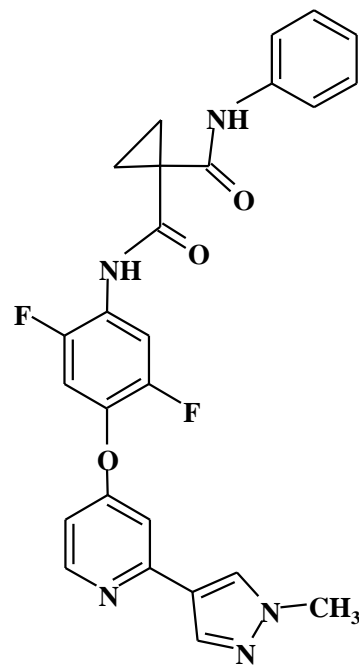
Most tyrosine kinase inhibitors target the ATP binding pocket.

KIT also has an interior pocket located between the N and C lobes of the kinase, which functions as a “switch pocket” (SP).

If the exon 11 juxtamembrane domain of KIT occupies this SP, the kinase adopts an inactive conformation. If the exon 17 activation loop occupies this SP, the kinase adopts a catalytically active conformation.

SP inhibitors were developed to block access to the SP and prevent KIT from adopting the catalytically active conformation.

DCC-2618



Deciphera:

DCC-2618 was designed to improve the treatment of GIST patients by inhibiting the full spectrum of mutations in KIT and PDGFRA, including the PDGFRA D842V mutation that drives a subset of GIST. Instead of targeting the ATP-binding pocket, DDC-2618 binds to the switch pocket.

It blocks a much wider range of mutations, including mutations in KIT exon 17 (which can cause secondary resistance) and PDGFRA D842V mutations.

In June 2017, findings were reported from the dose escalation stage of a Phase 1 trial of DCC-2618.

DCC-2618 was well tolerated at all doses up to 400 mg daily The majority of those enrolled were patients with GIST who had received an average of 3.4 prior TKI therapies. In GIST patients shown to harbor a broad range of KIT and PDGFRA mutations who received at least 100 mg of DCC-2618 daily, we observed a disease control rate of 85% (23 of 27 patients) at 8 weeks, 78% (18 of 23 patients) at 12 weeks and 60% (9 of 15 patients) at 24 weeks. ...

On Jan. 4, 2018, Deciphera announced the start of the Phase 3 “INVICTUS” trial of DCC-2618. This randomized trial is for GIST patients who have failed the three standard drugs for GIST, Gleevec, Sutent and Stivarga.

Plexxikon:

Optimizing kinase inhibitors to treat cancer

Fourth AACR International Conference on Frontiers in Basic Cancer Research; October 2015; Philadelphia

“KIT inhibitors are now standard therapy for advanced GISTs ... Even with multiple compounds approved, resistance mutations - in exon 17 in particular - still limit the durability of clinical benefit. We have discovered PLX9486 as an effective inhibitor of mutant KIT, including exon 17 mutations, with the added feature of selectivity versus the wild-type KIT kinase activity. This compound shows potent activity against exon 17 mutant tumors both in vitro and in vivo.”

CTOS 2017: A Phase 1 Pharmacokinetic and Pharmacodynamic Study of PLX9486, a Novel KIT Inhibitor with Potent Activity Against Exon 17/18 Activation Loop Mutations in Patients with GIST

*J. Trent, University of Miami Sylvester Cancer Center, Miami, Florida, USA
... G. Michelson, Clinical Development, Plexxikon, Berkeley, California, USA ...*

Objective: PLX9486 is a novel TKI with activity against the primary KIT mutations (ex 9 and 11) and against the activation loop mutations in ex 17 and 18.

Study objective: determine maximum tolerated dose (MTD) of PLX9486.

Conclusion: PLX9486 is a novel inhibitor of KIT with activity against difficult to treat ex resistance 17/18 mutations and demonstrates a favorable safety profile. ... Expansion cohorts in GIST are planned ...



Larotrectinib highly effective in (rare!) subset of wild-type GISTs carrying TRK mutations.

June 3, 2017 -- Loxo Oncology, Inc. today announced interim clinical data from all three ongoing larotrectinib (LOXO-101) clinical trials in patients whose tumors harbor tropomyosin receptor kinase (TRK) fusions. ... “Larotrectinib delivers consistent and durable responses in TRK fusion patients across all ages, regardless of tumor context, and does so with few side effects,” said David Hyman, M.D., chief of the early drug development service at Memorial Sloan Kettering Cancer Center, who will present the data at ASCO. “In this way, the larotrectinib TRK fusion story fulfills the promise of precision medicine, where tumor genetics rather than tumor site of origin define the treatment approach. It is now incumbent upon the clinical oncology and pathology communities to examine our testing paradigms, so that TRK fusions and other actionable biomarkers become part of the standard patient workup.” ... TRK fusions occur rarely but broadly in various adult and pediatric solid tumors, including ... GIST ...

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