2020 VIRTUAL MEETING

GIST Episode 2: Biology – Genetics – Pathology

Part A: basic knowledge for GIST patients

David Josephy, Life Raft Group Canada

david.josephy@liferaftgroup.ca

***Disclaimer**: I am not a physician. I am a scientist with some experience in cancer research. Nothing in this presentation should be regarded as medical advice or as a substitute for consulting with your doctors.*

TOPICS

- **Origin of GISTs: Interstitial cells of Cajal**
- ***KIT* oncogene and KIT protein**
- **“TKI” drugs (such as Gleevec) – how do they work?**

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

To determine the best treatment of a cancer, we need to know the type of cell from which it developed.

The cell type (not the organ) defines a cancer.

Basal cell carcinoma **and** ***melanoma*** **are both "skin cancers" but they are completely different diseases.**

Adenocarcinoma **and** ***mesothelioma*** **are both "lung cancers" but they are completely different diseases.**

Carcinomas vs sarcomas

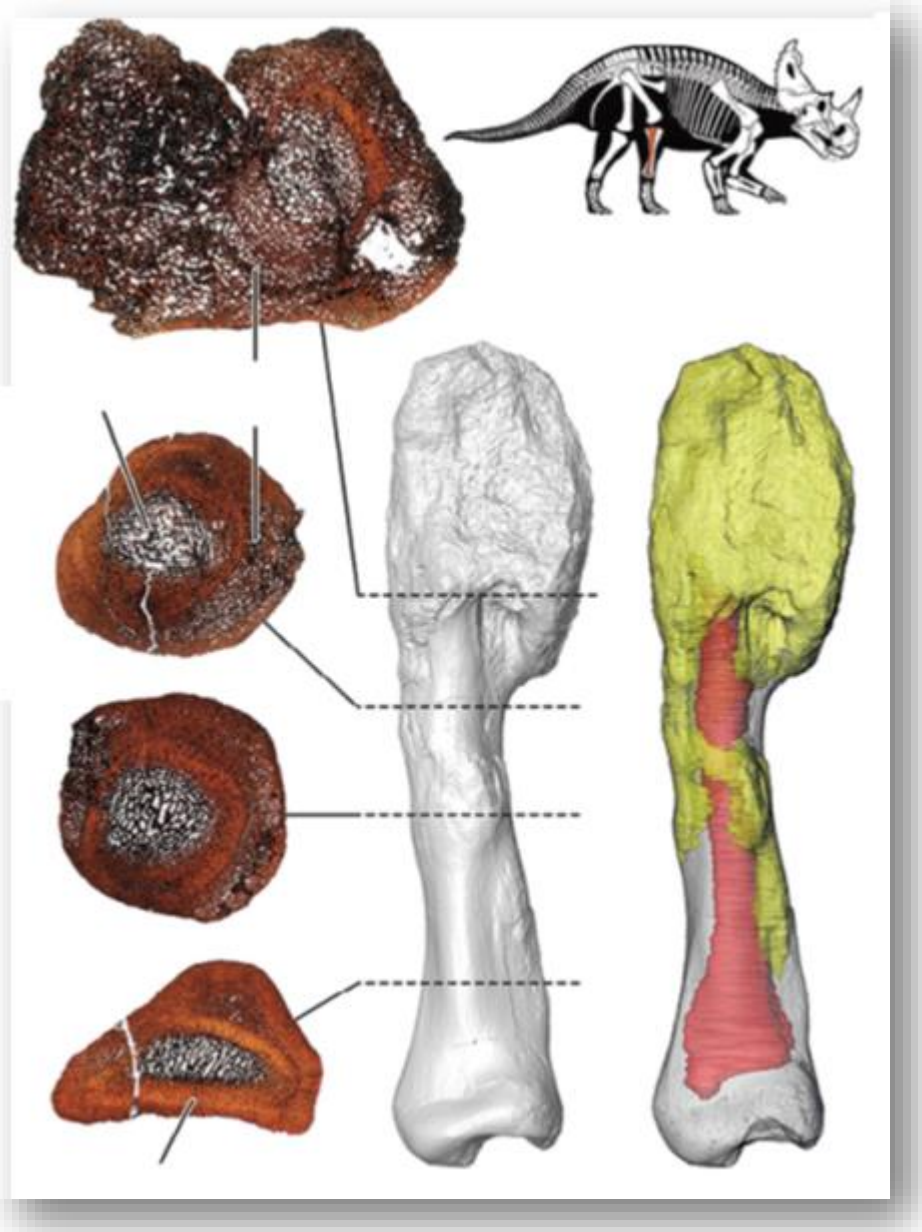
***Carcinomas** are cancers that arise in **epithelial** tissues: the skin or the tissues that line the organs. Examples: the common breast, colon, lung, pancreas, prostate, and stomach cancers.*

***Sarcomas** are cancers that arise in connective/ supportive tissues. Examples: osteosarcoma (bone); liposarcoma (fat); angiosarcoma (blood vessels).*

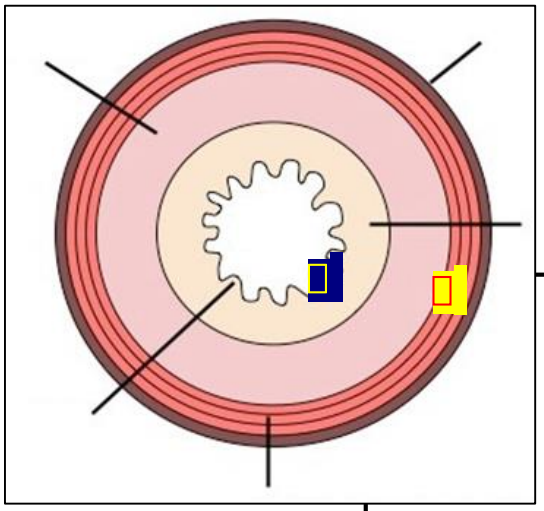
Sarcomas are rare (about 1% of cancers in human adults).

(Sarcomas are quite common in canines; e.g., osteosarcomas in Great Danes and German Shepherds; hemangiosarcomas in Boxers and Golden Retrievers.)

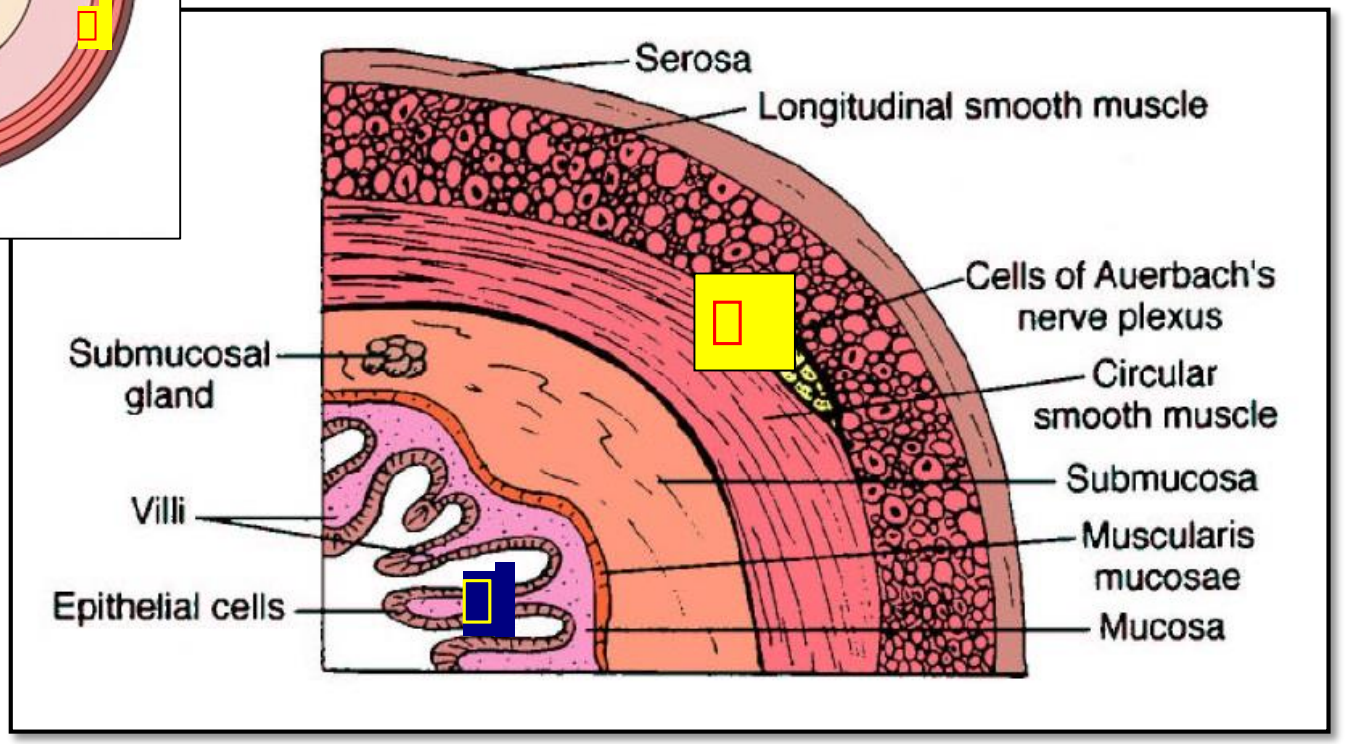
An osteosarcoma in a horned dinosaur, 77 million years ago; Ekhtiari *et al.*, *Lancet Oncology*, Aug. 2020.



Carcinoma vs sarcoma: Cross-section of the GI tract

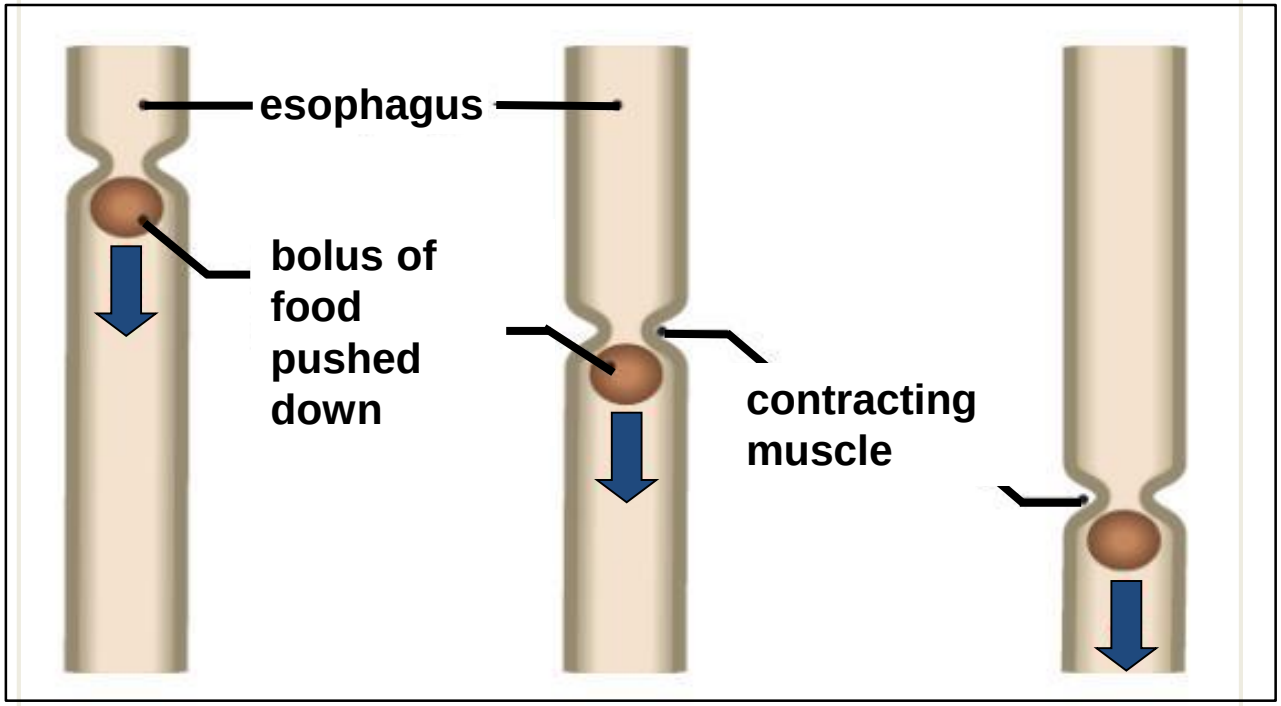


 GI carcinomas start in the epithelial lining (the body's "outside" surface)



 GISTs (sarcomas) start in the muscular wall

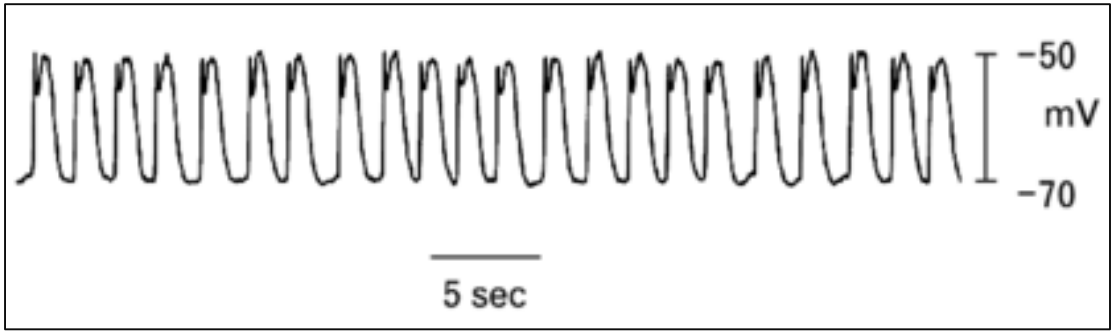
Peristalsis - the coordinated waves of muscle action that push food through the GI tract during digestion.



The coxswain keeps the crew's muscles synchronized.

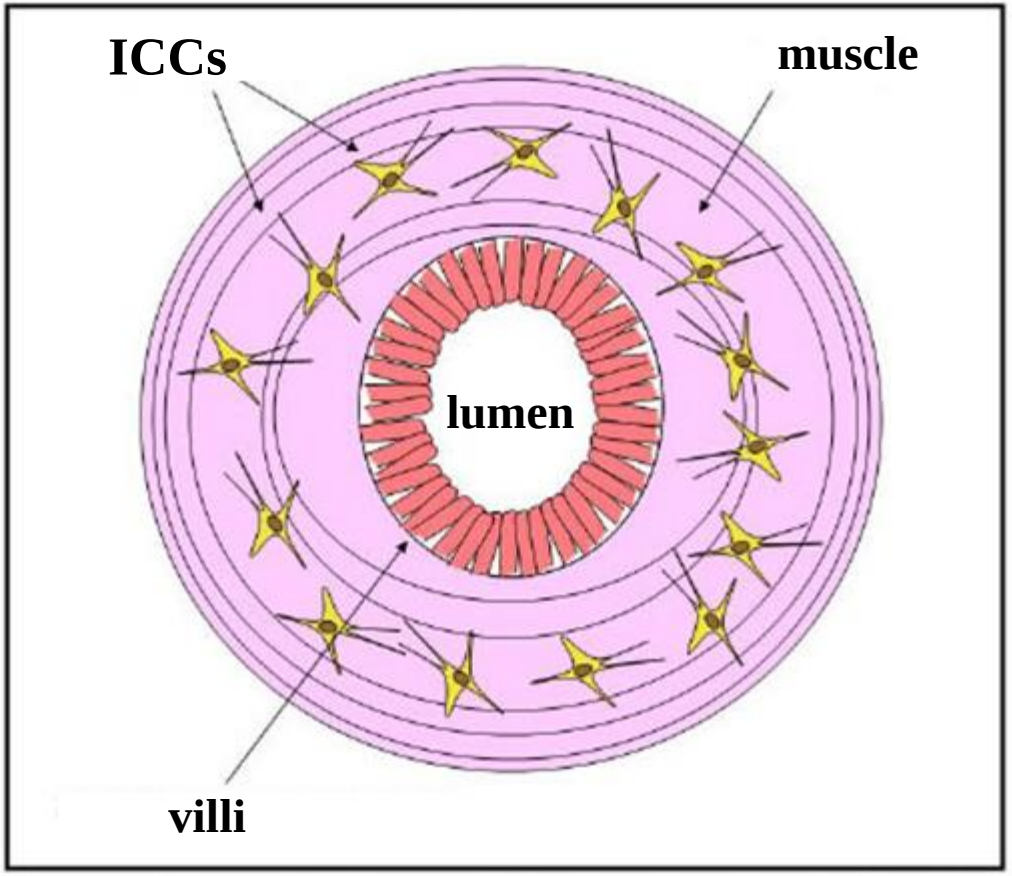
Interstitial Cells of Cajal are the "pacemaker" cells that coordinate GI tract peristalsis. ICCs send out the electrical pulses that stimulates the waves of contraction of the muscle surrounding the GI tract. ICCs are the cells where GISTs start.

ICCs: pacemaker electrical activity (mouse)



The coxswain keeps the crew's muscles synchronized.

Interstitial Cells of Cajal

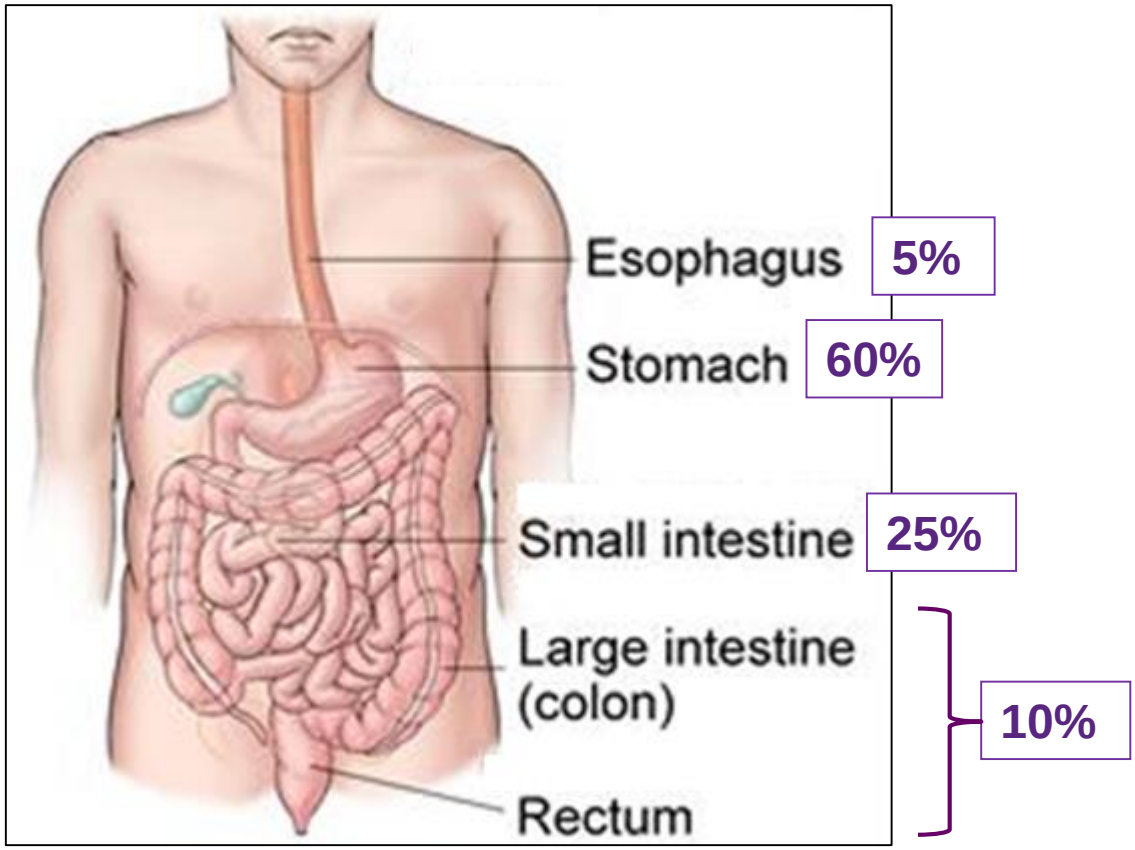


Ramon y Cajal (1852-1934)

liferaftgroup.org/2009/06/interstitial-cells-of-cajal-what-are-they-and-why-should-you-care/

Huizinga and Chen, Interstitial cells of Cajal: update on basic and clinical science, *Curr. Gastroenterol. Rep.* (2014)

Wherever they occur along the GI tract, GISTs arise in the same cell type, the ICC.



Metastasis:

At the time of diagnosis, a GIST may be localized or it may have spread (metastasized), *e.g.*, to the liver or lung.

GIST metastases are still GISTs and must be treated as GISTs

… they are not "liver cancer" or "lung cancer".

An Englishman in New York is still an Englishman.

The Molecular Biology of GIST

Proteins and Genes

Proteins are linear sequences of building blocks called *amino acids*, of which there are 20 types:

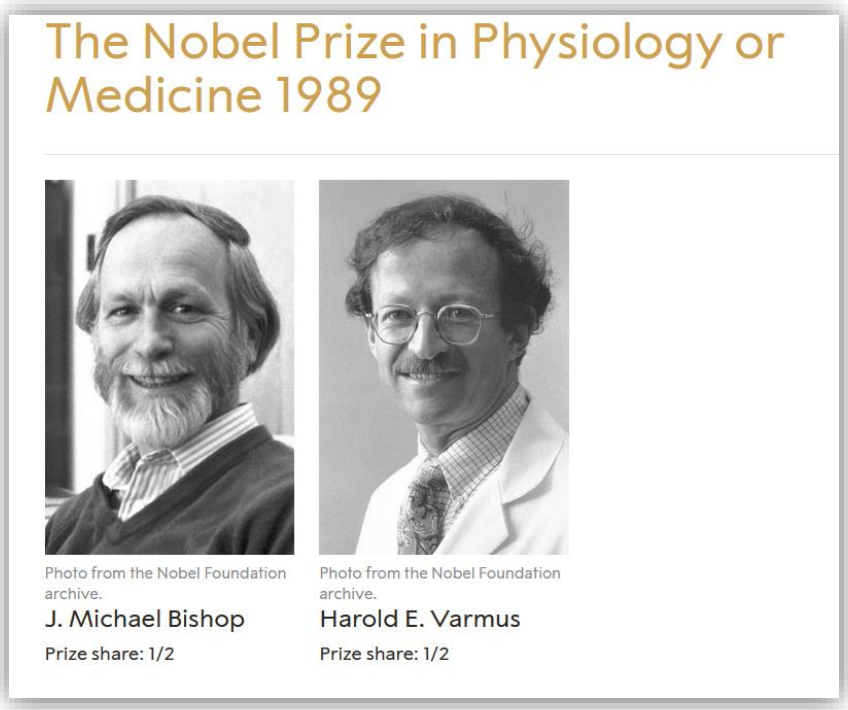
A = alanine	C = cysteine	D = aspartic acid
H = histidine	K = lysine	*etc*.

Length of protein amino acid sequences: anywhere from a few dozen to tens of thousands.

Genes (DNA) are the codes ("construction blueprints") for the cell's proteins. The human genome encodes >30,000 different proteins.

Oncogenes:

The concept of targeted cancer chemotherapy grew out of the discovery of *oncogenes*: genes which, when mutated, drive the uncontrolled growth of cancer cells. Turning this concept into reality took decades of research!



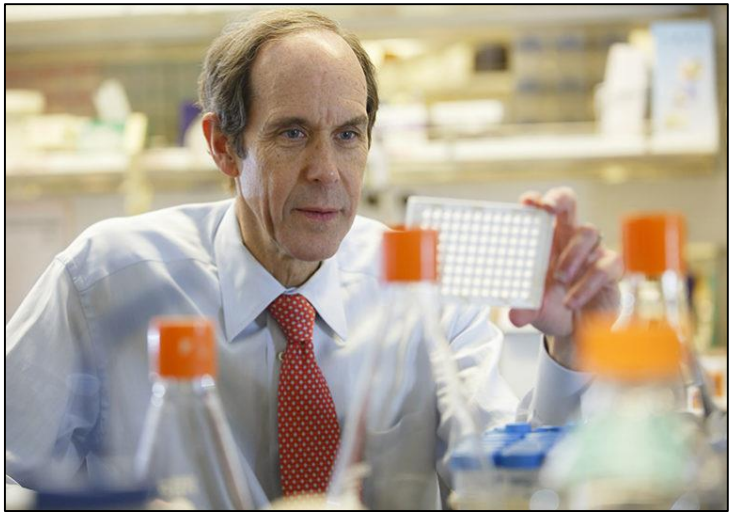
Imatinib was one of the first drugs targeting the protein product of an oncogene; imatinib was first used for treatment of CML (a type of leukemia; 1998) and, soon thereafter, for GIST.

STI571: Targeting BCR-ABL as Therapy for CML

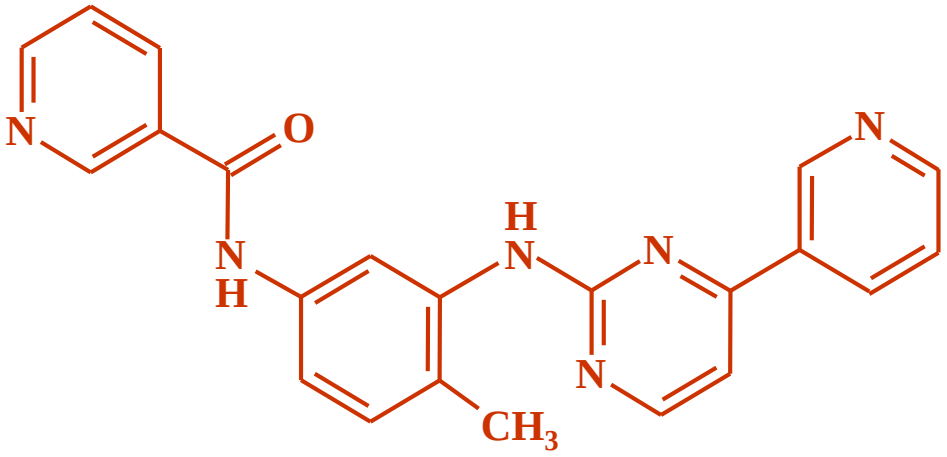
MICHAEL J. MAURO, BRIAN J. DRUKER

Leukemia Program, Division of Hematology and Medical Oncology, Oregon Health Sciences University, Portland, Oregon, USA

Key Words. *Chronic myelogenous leukemia · Tyrosine kinase · Philadelphia chromosome · STI571*



Brian Druker, OHSU



Imatinib (STI571; gleevec) inhibits ABL (product of the oncogene that drives CML)

In 1998, a breakthrough discovery - the role of the *KIT* oncogene - revolutionized GIST diagnosis and treatment.

Basic science research on the *KIT* gene laid the foundation for the breakthrough.

The Mouse *W*/c-*kit* Locus

A Mammalian Gene That Controls the Development of Three Distinct Cell Lineages[a]

PATRICE DUBREUIL, ROBERT ROTTAPEL, ALASTAIR D. REITH, LESLEY FORRESTER, AND ALAN BERNSTEIN[b]

Division of Molecular and Developmental Biology
Samuel Lunenfeld Research Institute at Mount Sinai Hospital
Toronto, Ontario, Canada, M5G 1X5

Alan Bernstein

The GIST-KIT connection: the 1998 breakthrough that revolutionized GIST diagnosis and treatment.

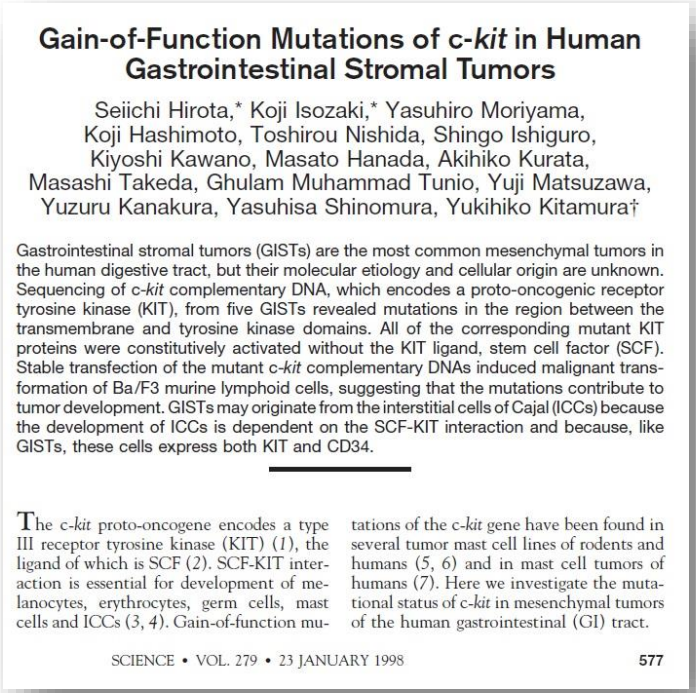
GIST cells almost always express a protein called "KIT".

(Very few other cells in the body express KIT.)

In most GISTs, the *KIT* gene (an oncogene) is mutated, producing an aberrant form of KIT protein that "drives" cell division and therefore drives the cancer.

Seiichi Hirota, M.D. Yukihiko Kitamura, M.D.

Osaka University Medical School



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

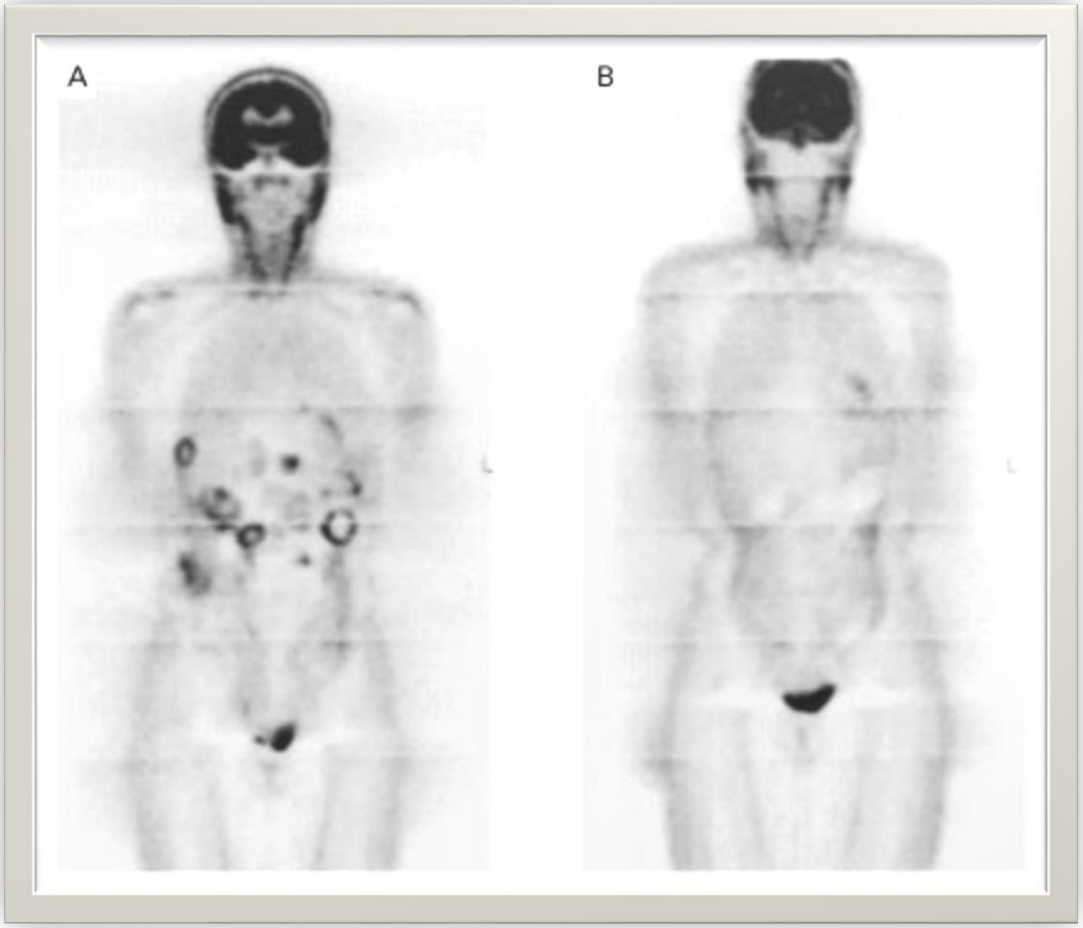
Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiko Kitamura†

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.

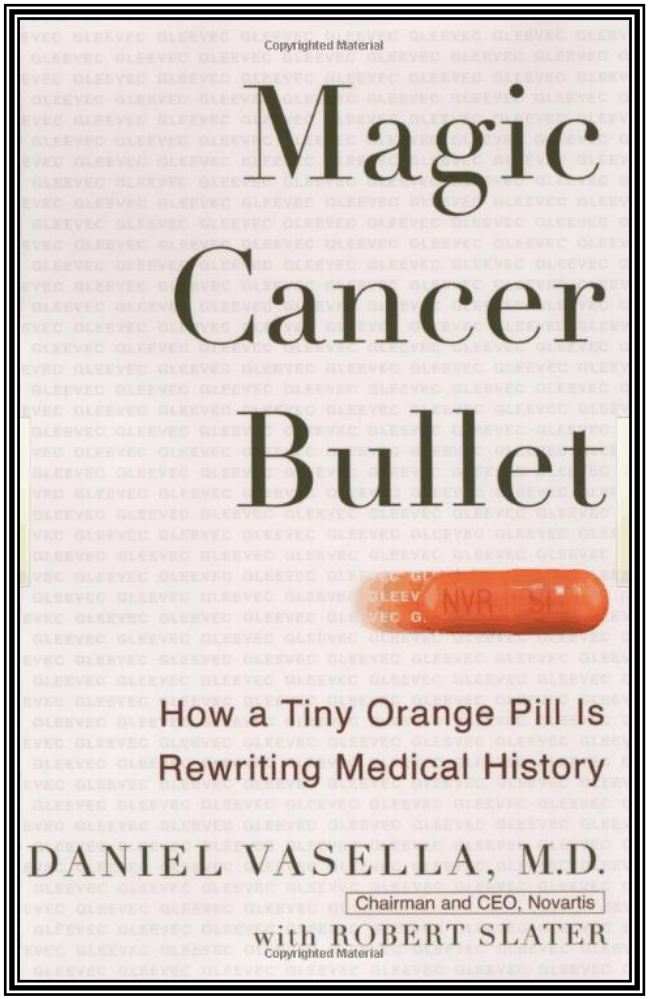
SCIENCE • VOL. 279 • 23 JANUARY 1998 577

Imatinib for GIST



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

Imatinib (gleevec) inhibits ABL (product of CML oncogene) and KIT (product of GIST oncogene)



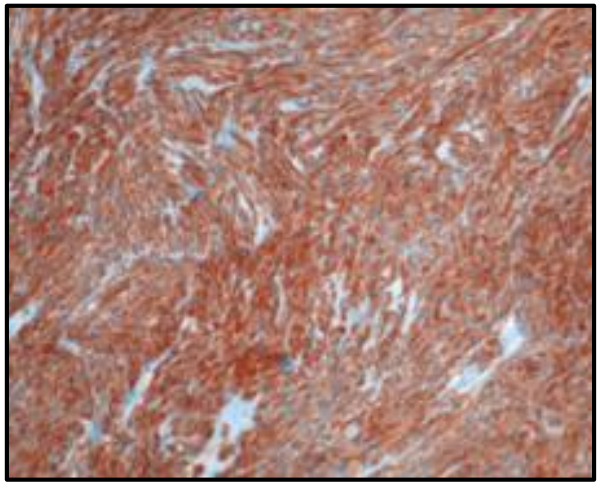
KIT ("c-Kit" or "CD117")

KIT protein is made (expressed) by only a few types of adult cells, including ICCs (and GISTs).

Immunohistochemistry (IHC):

The essential step in diagnosing GIST is to test whether the tumor cells express KIT.

The test is performed by *staining* the tissue sample (obtained at surgery) with an *antibody* that recognizes KIT protein. The stained tissue is examined under the microscope.



Di Vizio *et al.*, 2008

If the cells stain brown, they are almost certainly GIST.

SURGICAL PATHOLOGY REPORT

Ancillary Studies

Immunohistochemical Studies
KIT (CD117): Positive
DOG1 (ANO1): Positive
Other (specify): CD34 positive, Smooth muscle actin: negative, desmin: negative, S100: negative

IHC: The tumour expresses KIT (and DOG1), so it is almost certainly GIST.

Consistent with this evidence, the tumour does *not* express proteins (*e.g.*, desmin) that are typically expressed by sarcomas other than GIST.

The GIST-KIT connection (2020 update)

We now realize that "GIST" is an "umbrella" term that encompasses several sarcomas, differing at the molecular level.

Most GISTs are "*KIT*-mutant", but about 25% are *not*: they carry (and express) the "wild-type" (normal) form of KIT.

- About 15% have a mutation in a related gene, *PDGFR*.

- A few have mutations in another gene, *e.g.* *RAS*, *BRAF*, *NF1*, *NTRK*, or *SDH* …. and probably a few others, still unknown.

These less-common forms of GIST are distinct from *KIT*-mutant GIST, in terms of their biology and treatment.

***Note*: All of these forms of GIST are derived from ICCs and they all* express KIT protein – whether or not the *KIT* gene is mutated.**

***almost* all, anyway; there are rare exceptions.**

Immunohistochemistry (IHC) *vs*. Mutational testing: Different tests, different questions, different answers

	Immunohistochemistry (staining for KIT protein)	Mutational testing (DNA sequencing of *KIT* gene)
Tests for:	expression of KIT protein by the tumour cells	mutations in the *KIT* gene in the tumour cell DNA
Tells us:	whether the tumour is a GIST (often, merely confirming the diagnosis)	whether the tumour is a KIT-mutant GIST (and, if so, identifies the mutation)*
Requires:	tumour sample (biopsy or surgery)	tumour sample (*e.g.*, FFPE: Formalin-Fixed Paraffin-Embedded)
Performed by pathology lab?	always	sometimes; LRG strongly recommends that patients push to have mut. testing done!

*If no mutation is seen in the *KIT* gene, the lab will probably go on to look at other genes, *e.g. PDGFR, RAS, BRAF* …

Protein structure: Exons

Many proteins consist of several distinct *domains (sub-structures), each ≈30-100 amino acids:**

Each domain corresponds to a separate segment of the gene coding for that protein; these gene segments are called exons. The *KIT* gene has 21 exons.

Genome: Library
Protein: Book
Exon/Domain: Chapter
Amino acid: Letter

this is an over-simplified discussion of exons and domains

The KIT protein: 976 amino acid residues

```
1   MRGARGAWDF LCVLLLLLRV QTGSSQPSVS PGEPSPPSIH PGKSDLIVRV GDEIRLLCTD
61  PGFVKWTFEI LDETNENKQN EWITEKAEAT NTGKYTCTNK HGLSNSIYVF VRDPAKLFLV
121 DRSLYGKEDN DTLVRCPLTD PEVTNYSLKG CQGKPLPKDL RFIPDPKAGI MIKSVKRAYH
181 RLCLHCSVDQ EGKSVLSEKF ILKVRPAFKA VPVVSVSKAS YLLREGEEFT VTCTIKDVSS
241 SVYSTWKREN SQTKLQEKYN SWHHGDFNYE RQATLTISSA RVNDSGVFMC YANNTFGSAN
301 VTTTLEVVDK GFINIFPMIN TTVFVNDGEN VDLIVEYEAF PKPEHQQWIY MNRTFTDKWE
361 DYPKSENESN IRYVSELHLT RLKGTEGGTY TFLVSNSDVN AAIAFNVYVN TKPEILTYDR
421 LVNGMLQCVA AGFPEPTIDW YFCPGTEQRC SASVLPVDVQ TLNSSGPPFG KLVVQSSIDS
481 SAFKHNGTVE CKAYNDVGKT SAYFNFAFKG NNKEQIHPHT LFTPLLIGFV IVAGMMCIIV
541 MILTYKYLQK PMYEVQWKVV EEINGNNYVY IDPTQLPYDH KWEFPRNRLS FGKTLGAGAF
601 GKVVEATAYG LIKSDAAMTV AVKMLKPSAH LTEREALMSE LKVLSYLGNH MNIVNLLGAC
661 TIGGPTLVIT EYCCYGDLLN FLRRKRDSFI CSKQEDHAEA ALYKNLLHSK ESSCSDSTNE
721 YMDMKPGVSY VVPTKADKRR SVRIGSYIER DVTPAIMEDD ELALDLEDLL SFSYQVAKGM
781 AFLASKNCIH RDLAARNILL THGRITKICD FGLARDIKND SNYVVKGNAR LPVKWMAPES
841 IFNCVYTFES DVWSYGIFLW ELFSLGSSPY PGMPVDSKFY KMIKEGFRML SPEHAPAEMY
901 DIMKTCWDAD PLKRPTFKQI VQLIEKQISE STNHIYSNLA NCSPNRQKPV VDHSVRINSV
961 GSTASSSQPL LVHDDV
```

The KIT protein: 21 exons

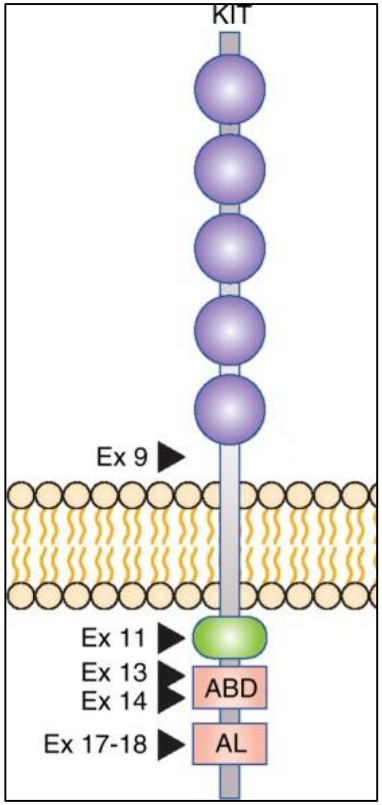
```
    1                                                                  2
1   MRGARGAWDF LCVLLLLLRV QTGSSQPSVS PGEPSPPSIH PGKSDLIVRV GDEIRLLCTD
                                                                     3
61  PGFVKWTFEI LDETNENKQN EWITEKAEAT NTGKYTCTNK HGLSNSIYVF VRDPAKLFLV
121 DRSLYGKEDN DTLVRCPLTD PEVTNYSLKG CQGKPLPKDL RFIPDPKAGI MIKSVKRAYH
                                          4
181 RLCLHCSVDQ EGKSVLSEKF ILKVRPAFKA VPVVSVSKAS YLLREGEEFT VTCTIKDVSS
                    5
241 SVYSTWKREN SQTKLQEKYN SWHHGDFNYE RQATLTISSA RVNDSGVFMC YANNTFGSAN
                6                                                  8
301 VTTTLEVVDK GFINIFPMIN TTVFVNDGEN VDLIVEYEAF PKPEHQQWIY MNRTFTDKWE
              7
361 DYPKSENESN IRYVSELHLT RLKGTEGGTY TFLVSNSDVN AAIAFNVYVN TKPEILTYDR
                                        9
421 LVNGMLQCVA AGFPEPTIDW YFCPGTEQRC SASVLPVDVQ TLNSSGPPFG KLVVQSSIDS
                                                10
481 SAFKHNGTVE CKAYNDVGKT SAYFNFAFKG NNKEQIHPHT LFTPLLIGFV IVAGMMCIIV
                11                                                 12
541 MILTYKYLQK PMYEVQWKVV EEINGNNYVY IDPTQLPYDH KWEFPRNRLS FGKTLGAGAF
                                          13
601 GKVVEATAYG LIKSDAAMTV AVKMLKPSAH LTEREALMSE LKVLSYLGNH MNIVNLLGAC
          14                                                      15
661 TIGGPTLVIT EYCCYGDLLN FLRRKRDSFI CSKQEDHAEA ALYKNLLHSK ESSCSDSTNE
                                    16
721 YMDMKPGVSY VVPTKADKRR SVRIGSYIER DVTPAIMEDD ELALDLEDLL SFSYQVAKGM
            17                                                 18
781 AFLASKNCIH RDLAARNILL THGRITKICD FGLARDIKND SNYVVKGNAR LPVKWMAPES
                                    19                             20
841 IFNCVYTFES DVWSYGIFLW ELFSLGSSPY PGMPVDSKFY KMIKEGFRML SPEHAPAEMY
                                          21
901 DIMKTCWDAD PLKRPTFKQI VQLIEKQISE STNHIYSNLA NCSPNRQKPV VDHSVRINSV
961 GSTASSSQPL LVHDDV
```

The KIT protein: exons 9 and 11

```
1    MRGARGAWDF LCVLLLLLRV QTGSSQPSVS PGEPSPPSIH PGKSDLIVRV GDEIRLLCTD
61   PGFVKWTFEI LDETNENKQN EWITEKAEAT NTGKYTCTNK HGLSNSIYVF VRDPAKLFLV
121  DRSLYGKEDN DTLVRCPLTD PEVTNYSLKG CQGKPLPKDL RFIPDPKAGI MIKSVKRAYH
181  RLCLHCSVDQ EGKSVLSEKF ILKVRPAFKA VPVVSVSKAS YLLREGEEFT VTCTIKDVSS
241  SVYSTWKREN SQTKLQEKYN SWHHGDFNYE RQATLTISSA RVNDSGVFMC YANNTFGSAN
301  VTTTLEVVDK GFINIFPMIN TTVFVNDGEN VDLIVEYEAF PKPEHQQWIY MNRTFTDKWE
361  DYPKSENESN IRYVSELHLT RLKGTEGG[Exon 9]LVSNSDVN AAIAFNVYVN TKPEILTYDR
421  LVNGMLQCVA AGFPEPTIDW YFCPGTEQRC SASVLPVDVQ TLNSSGPPFG KLVVQSSIDS
481  SAFKHNGTVE CKAYNDVGKT SAYFNFAFKG NNKEQIHPHT LFTPLLIGFV IVAGMMCIIV
541  MILTYKYLQK PMYEVQWKVV EEINGNNYVY IDPTQLPYDH KWEFPRNRLS FGKTLGAGAF
601  GKVVEATAY[Exon 11]AAMTV AVKMLKPSAH LTEREALMSE LKVLSYLGNH MNIVNLLGAC
661  TIGGPTLVIT EYCCYGDLLN FLRRKRDSFI CSKQEDHAEA ALYKNLLHSK ESSCSDSTNE
721  YMDMKPGVSY VVPTKADKRR SVRIGSYIER DVTPAIMEDD ELALDLEDLL SFSYQVAKGM
781  AFLASKNCIH RDLAARNILL THGRITKICD FGLARDIKND SNYVVKGNAR LPVKWMAPES
841  IFNCVYTFES DVWSYGIFLW ELFSLGSSPY PGMPVDSKFY KMIKEGFRML SPEHAPAEMY
901  DIMKTCWDAD PLKRPTFKQI VQLIEKQISE STNHIYSNLA NCSPNRQKPV VDHSVRINSV
961  GSTASSSQPL LVHDDV
```

Exon 11 encodes the “juxtamembrane” domain of the KIT protein.

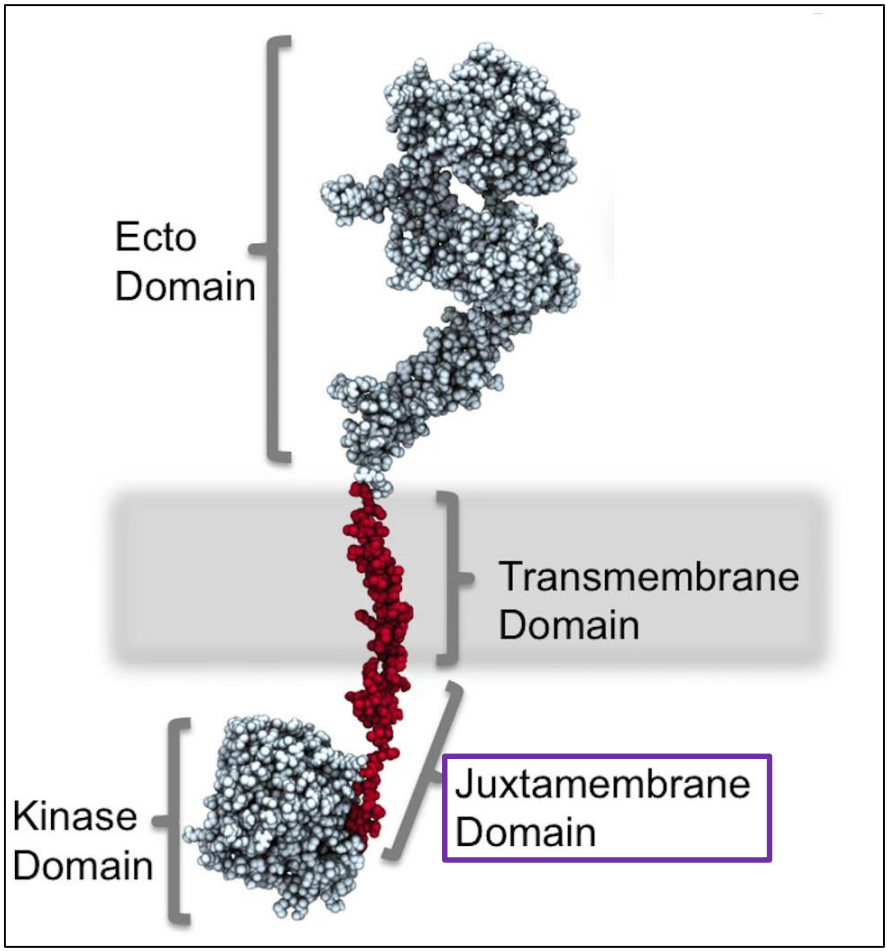
Exon 11 mutations cause a conformational change (“switch”) of KIT protein from its “inactive” to its “active” form, signaling the GIST cell to grow and divide.



Extracellular Ig-like domains

Juxtamembrane domain

Kinase domains



2020 VIRTUAL MEETING

GIST Episode 2: Biology – Genetics – Pathology

Part B: deeper information for patient advocates

David Josephy, Life Raft Group Canada

david.josephy@liferaftgroup.ca

***Disclaimer**: I am not a physician. I am a scientist with some experience in cancer research. Nothing in this presentation should be regarded as medical advice or as a substitute for consulting with your doctors.*

KIT mutations

KIT **is an "oncogene" - a gene which, when mutated, encodes a protein product that can instruct the cell to keep on dividing: a "stuck gas pedal".**

When the *KIT* gene is mutated, KIT protein acts as a "driver" that tells the GIST cells to proliferate.

KIT protein is an enzyme – a "tyrosine kinase" – that acts on other proteins, triggering a "signal transduction cascade". Inhibiting (shutting off) KIT activity is the mechanism of action of imatinib.

In ~75% of GIST cases – *but not 100%* – the *KIT* gene is mutated and "drives" tumour growth. Even in the remaining cases, such as "wild-type" GIST, inhibiting KIT *might* have some therapeutic benefit (?).

KIT mutations in GIST are (almost always) somatic.

The "driver" mutations in GISTs are almost always *somatic* – not *germ-line* – mutations.

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

Diversity of mutations in GISTs

GIST "driver" mutations can occur at many different sites in the *KIT* gene, affecting many different sites in the KIT protein … and sometimes GIST driver mutations occur in genes other than *KIT*: *PDGFR*, *SDH*, *BRAF*, *NTRK*, etc.

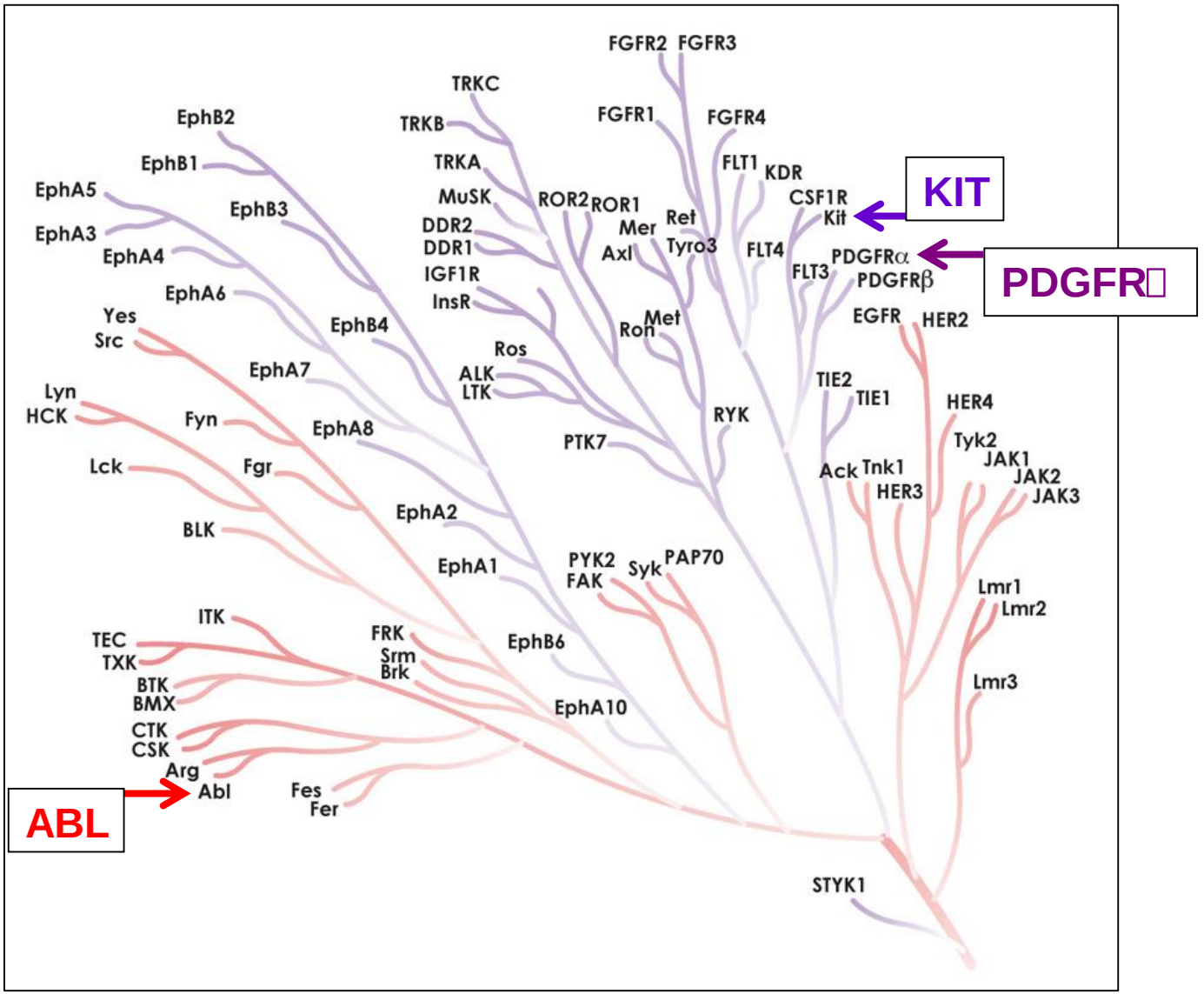
The site of the mutation affects prognosis and the response to drugs.

Mutation testing should be performed on all new GIST cases; a sample of the tumour is needed (not just a blood sample).

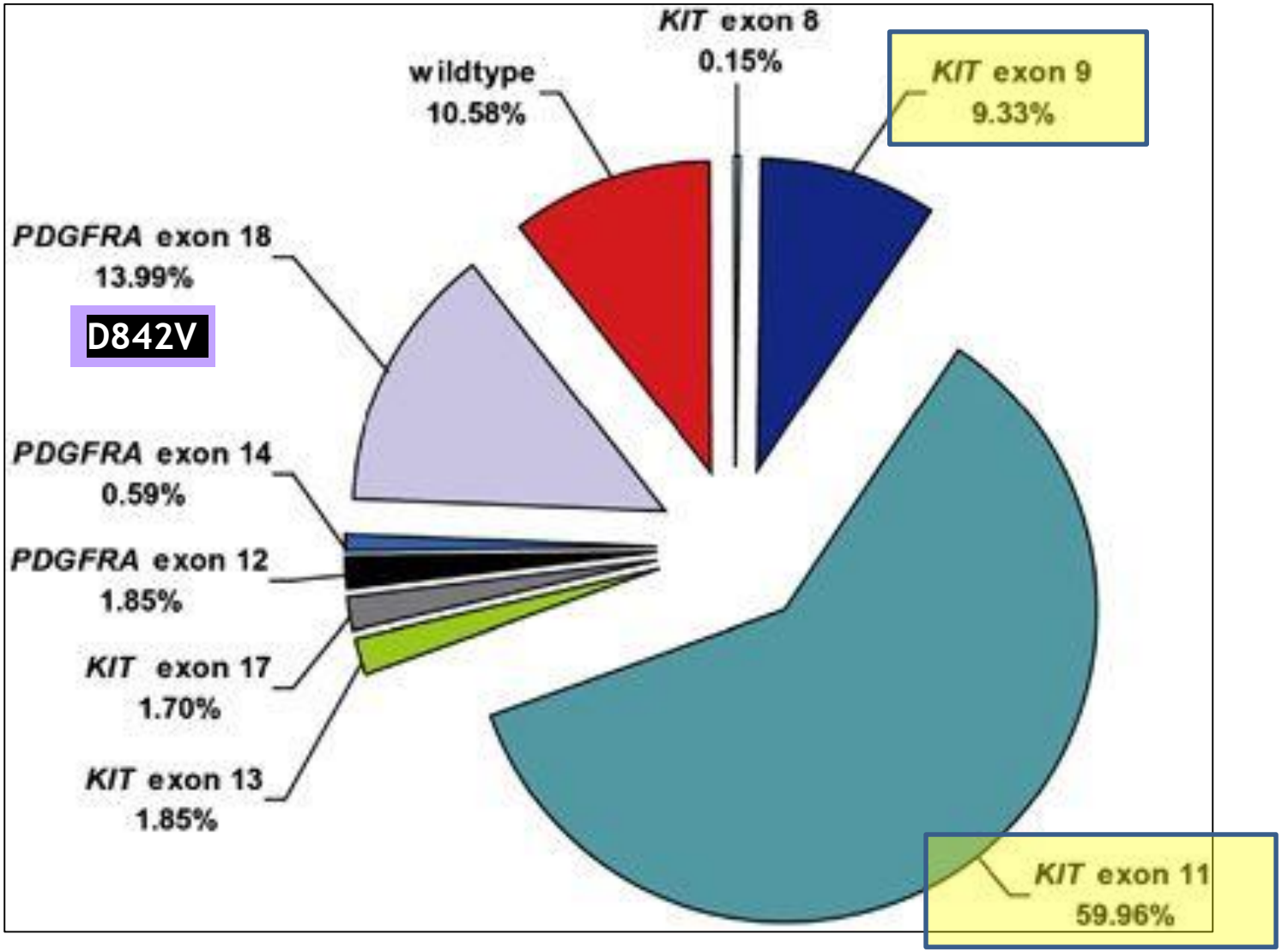
(Baveno declaration, 2008).

KIT is one member of a large family of related proteins. PDGFR□ is a "sister"; ABL is a "distant cousin".

human tyrosine kinases



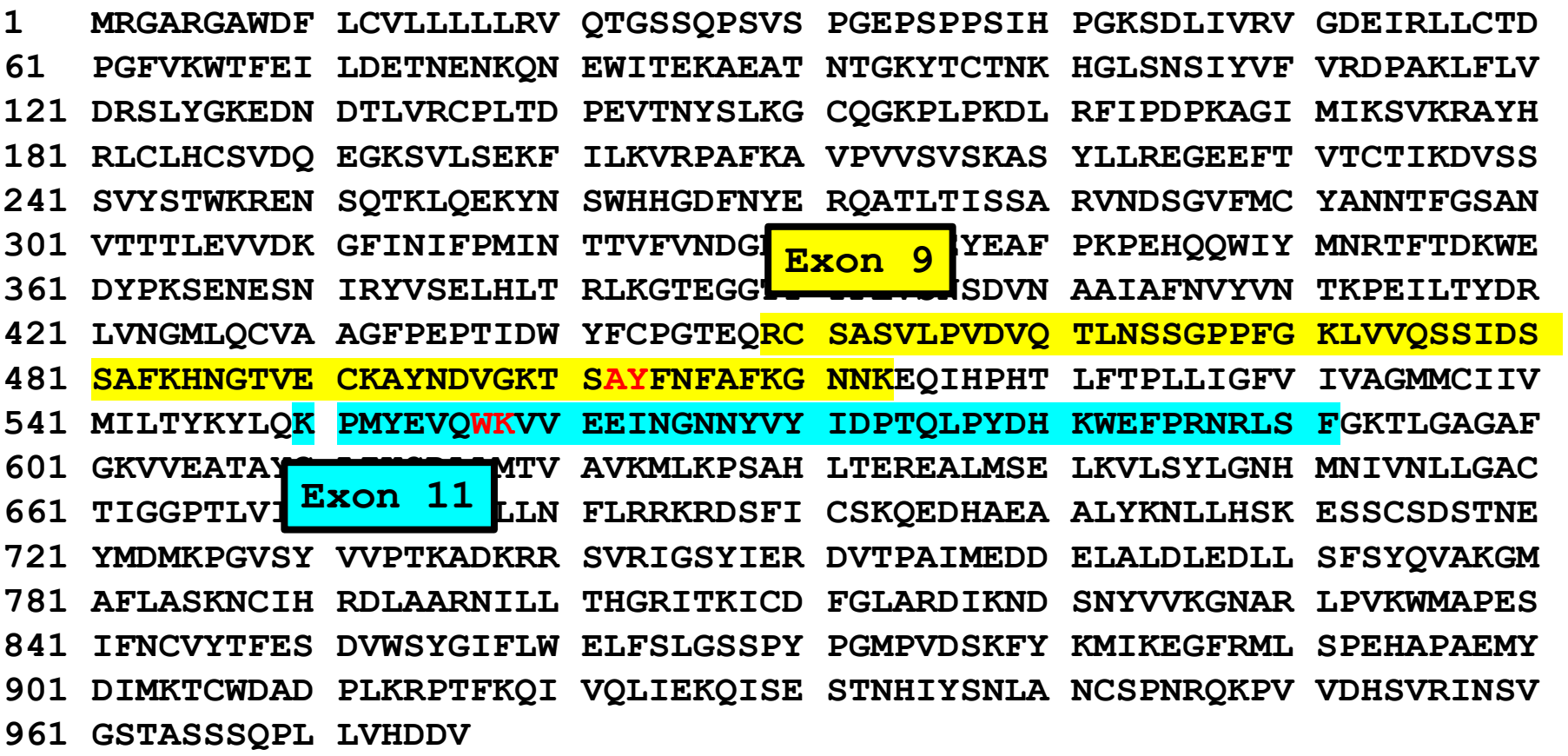
KIT mutations drive *most* sporadic GISTs.



***Huss et al., Modern Pathology* 26, 1004-1012 (2013)**

The KIT protein: 21 exons

Exons 9 and 11 are the regions of the KIT gene where the primary mutations in GISTs are most often found.



Understanding mutation terminology

What does "KIT V560D" mean?

This is a "mis-sense" mutation. Because of a mutation in the GIST cell's DNA, the 560th amino acid (building block) in the KIT protein has changed from the normal valine (V) to a different residue, aspartic acid (D).

What does "KIT W557_K558 del" mean?

This is a "deletion" mutation. Because of a mutation in the GIST cell's DNA, the 557th and 558th amino acids in the KIT protein are absent.

Targeted drugs for treating GIST

Chronic Myelogenous Leukemia (CML)

CML is a rare leukemia (cancer of the blood); CML 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 "distant cousin" of *KIT*.

ABL is a "tyrosine kinase" enzyme.

Drugs that inhibit (shut down) tyrosine kinases are "tyrosine kinase inhibitors" (TKIs).

GIST therapy has benefited from CML discoveries.

KIT and PDGFR□, like ABL, are *tyrosine kinase* enzymes.

The "first generation" GIST drugs – imatinib, sunitinib, and regorafenib – were all developed for CML or other cancers, not for GIST – but they work pretty well for GIST, too.

(A "second generation" of "bespoke" GIST drugs is arriving!)

The first three TKIs approved for use in GIST:

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

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

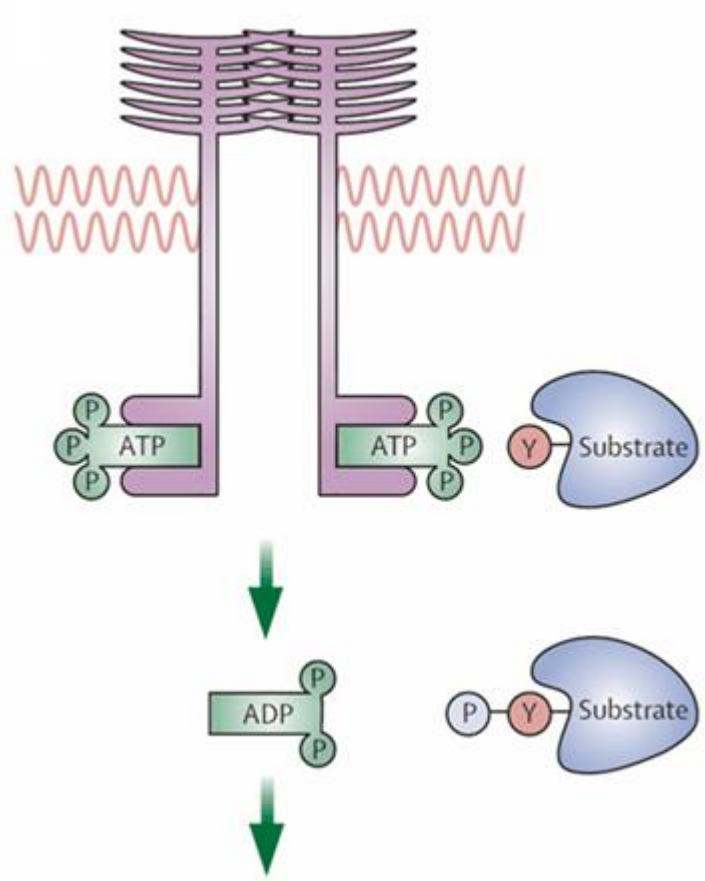
Third-line: Regorafenib (Stivarga - Bayer; 2013)

(The 'ib" ending indicates an enzyme inhibitor)

Imatinib, sunitinib, and regorafenib all act by the same mechanism – blocking the binding of ATP (cellular fuel) to KIT.

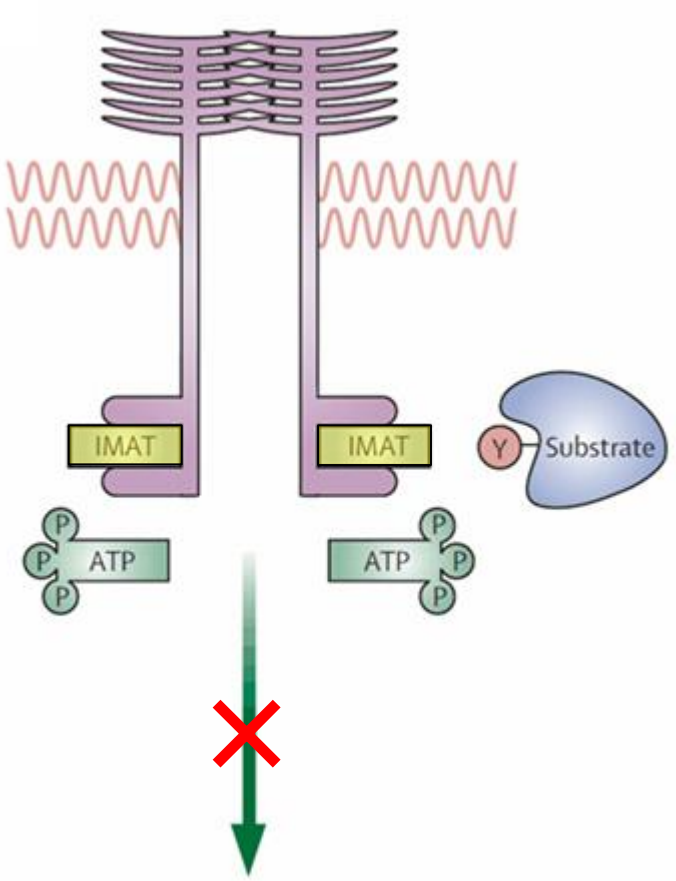
"Second generation" GIST drugs, such as ripretinib, use different mechanisms of KIT inhibition.

untreated



KIT-activated signal transduction;
GIST proliferation and survival

imatinib



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

Rubin *et al.*, *Lancet* 2007

Despite the success of these drugs, more are needed:

- **Some GISTs are imatinib-resistant from the outset; *e.g.*, the most common PDGFR□ mutation, D842V.**

- **Tolerance of the drugs (side effects) is variable.**

- **Imatinib halts the growth of most GISTs, but does not eliminate them; over time, GIST tumours tend to become imatinib-resistant, mainly due to additional mutations arising in the metastases.**

GIST subtypes and their treatment*

Mutation testing is <u>required</u> for <u>optimal</u> treatment of GIST patients.

<u>Primary mutations</u>:

1. KIT exon 11	**imatinib 400 mg**
2. KIT exon 9	**imatinib 800 mg (or tolerated dose)**
3. PDGFR□ D842V	**avapritinib**
4. SDH-deficient	**sunitinib or regorafenib (temozolomide trial?)**
5. Raf V600E	**Raf inhibitor**
6. Nf-1, Ras	**Raf or Mek inhibitor**
7. PI3K	**mTOR inhibitor**
8. IGF-1R-expressing	**IGF-1R inhibitor trial**
9. TRK fusion	**larotrectanib**

<u>Imatinib resistance mutations</u>:

exon 13 (ATP binding site)	**sunitinib 37.5 mg**
exon 17 (Activation loop)	**regorafenib or ripretinib**

****adapted from Dr. Jon Trent, presentation at LifeFest 2020***

Farag *et al*., Revolutions in treatment options in GISTs: the latest updates, *Curr. Treat. Options Oncol*. 2020

The treatment of advanced GIST is rapidly evolving with the development of novel molecular compounds such as avapritinib and ripretinib …

The availability of over five lines of treatment for patients with advanced GIST is likely to completely shift the current second-line and third-line treatment options …

For GIST patients with tumours harbouring a D842V mutation in PDGFR exon 18, avapritinib … will become first-line therapy for this molecular subgroup.

For second- and third-line treatment, results are awaited of a number of clinical trials. However, second-line and further treatment could potentially be tailored depending on secondary mutations found in imatinib-resistant GISTs. …

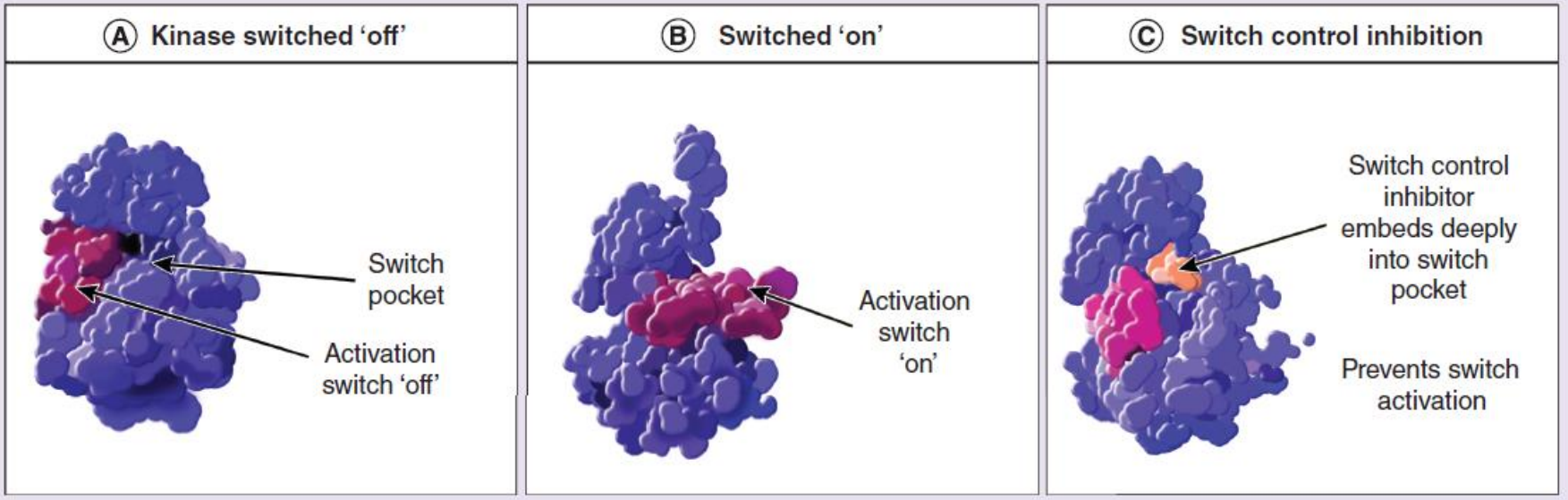
“Bespoke” TKI drugs for GIST

Qinlock™ (ripretinib; DCC 2618)

Deciphera Pharmaceuticals

May 15, 2020: FDA approved ripretinib for adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib.

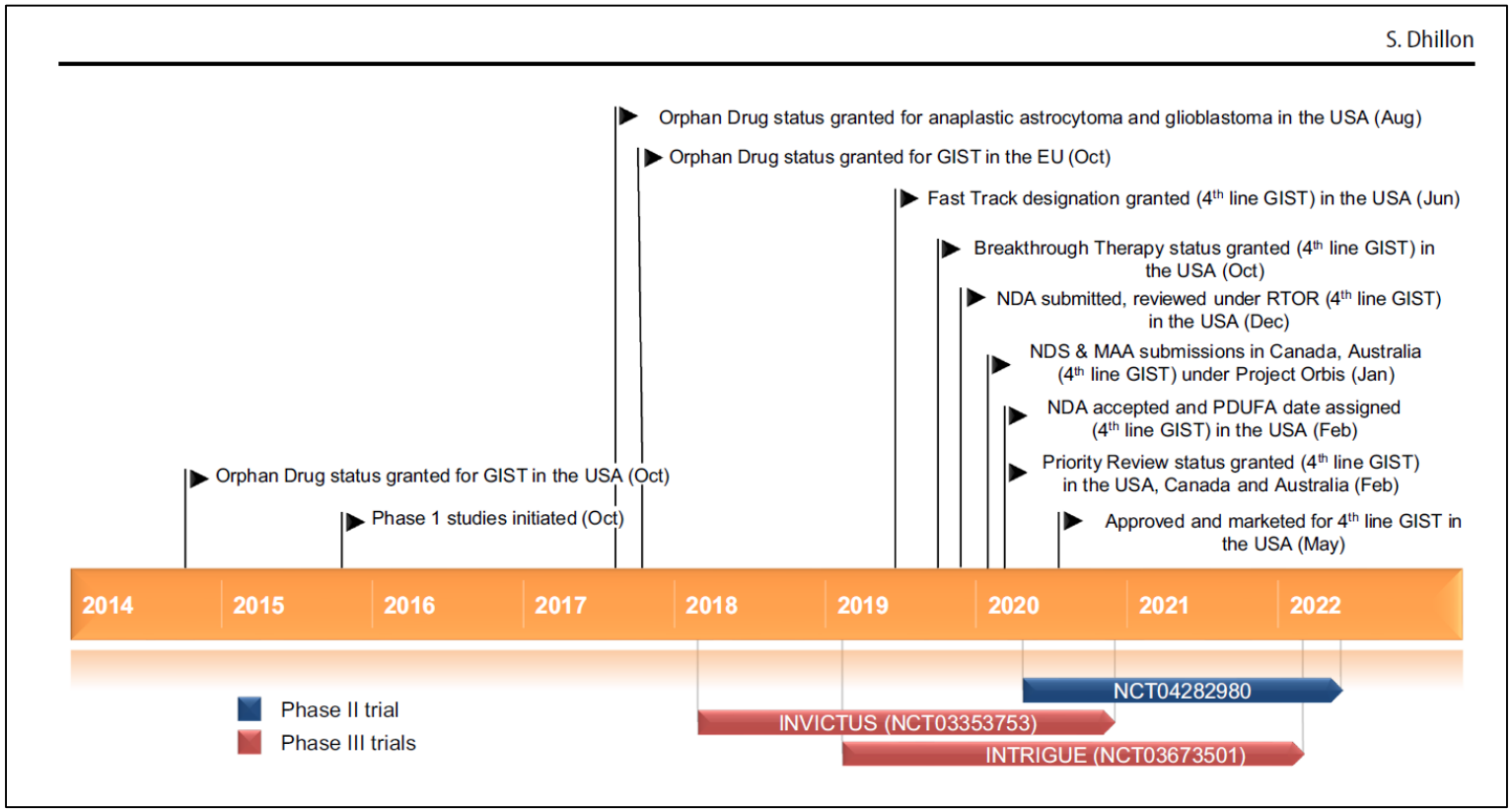
Ripretinib is a "switch-pocket" inhibitor; binds to KIT and prevents the protein from switching into its "active" conformation.



Nemunaitis *et al.*, 2020

Imatinib cuts the fuel line to the engine; ripretinib jams the piston.

QINLOCK™
(ripretinib) 50 mg tablets



Dhillon, S., Drugs (2020)

“Bespoke” TKI drugs for GIST

AYVAKIT™ (avapritinib; BLU-285)

Cambridge, Mass., June 29, 2020

Blueprint Medicines Corporation today announced that *The Lancet Oncology* published data from the NAVIGATOR clinical trial showing an unprecedented overall survival rate for AYVAKIT™ (avapritinib) in patients with advanced PDGFR□ D842V mutant GIST.

Michael Heinrich, M.D., Professor of Medicine at Oregon Health & Science University and primary author of the paper, said:

“It's tremendously rewarding to be able to offer - for the first time - a highly effective treatment option to my patients with PDGFR□ D842V mutant GIST.”

“AYVAKIT has become the new standard of care for patients with unresectable or metastatic GIST harboring a PDGFR□ exon 18 mutation,” said Andy Boral, M.D., Ph.D., Chief Medical Officer at Blueprint.

"The results of NAVIGATOR highlight the crucial role of gene testing in the diagnosis and treatment of GIST. Despite decreasing costs of single gene and next-generation sequencing panels, frequencies of genetic testing remain low among newly diagnosed patients with GIST. …

Avapritinib could potentially improve the disease course of metastatic PDGFR□ D842V-mutant GIST, which previously had a dire prognosis. Failure to treat this subgroup as a result of inadequate gene profiling represents a truly missed opportunity.

These findings provide additional evidence supporting the paradigm shift towards precision oncology and emphasise the usefulness of genomic sequencing in the personalisation of therapy for improving outcomes for patients with GIST."

Nguyen, Banerjee, and Sicklick, Moving gastrointestinal stromal tumours towards truly personalised precision therapy, *Lancet Oncology*, July 1, 2020

Drilon, A., TRK inhibitors in TRK fusion-positive cancers, *Ann. Oncol.* 2019.

TRK fusions are oncogenic drivers of various adult and paediatric cancers. The first-generation TRK inhibitors, larotrectinib and entrectinib, were granted landmark, tumour-agnostic regulatory approvals … in 2018 and 2019, respectively. Brisk and durable responses are achieved. …

These next-generation drugs are currently available in the clinic and proof-of-concept responses have been reported.

(ETV6-NTRK mutations are known - but very rare - driver mutations in GIST.)

On the horizon …. AZD3229

Banks *et al*., Discovery and pharmacological characterization of AZD3229, a potent KIT/PDGFRα inhibitor for treatment of gastrointestinal stromal tumors, *Sci. Transl. Med*., 2020.

We report the discovery and pharmacological characterization of AZD3229, a potent and selective small-molecule inhibitor of KIT and PDGFRα designed to inhibit a broad range of primary and imatinib-resistant secondary mutations seen in GIST. In engineered and GIST-derived cell lines, AZD3229 is 15 to 60 times more potent than imatinib in inhibiting KIT primary mutations …

AZD3229 has a superior potency and selectivity profile [and] has the potential to be a best-in-class inhibitor for clinically relevant KIT/PDGFRα mutations in GIST.

David Josephy
Life Raft Group Canada

david.josephy@liferaftgroup.ca