

Gastrointestinal stromal tumours: origin and molecular oncology

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Abstract | Gastrointestinal stromal tumours (GISTs) are a paradigm for the development of personalized treatment for cancer patients. The nearly simultaneous discovery of a biomarker that is reflective of their origin and the presence of gain-of-function kinase mutations in these tumours set the stage for more accurate diagnosis and the development of kinase inhibitor therapy. Subsequent studies of genotype and phenotype have led to a molecular classification of GIST and to treatment optimization on the basis of molecular subtype. The study of drug-resistant tumours has advanced our understanding of kinase biology, enabling the development of novel kinase inhibitors. Further improvements in GIST treatment may require targeting GIST stem cell populations and/or additional genomic events.

Type III receptor tyrosine kinase

A family of kinases sharing a structure that consists of five extracellular immunoglobulin-like domains, a transmembrane domain and a split kinase domain.

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumour of the gastrointestinal tract. Studies across the world show remarkably consistent annual incidences of 11 to 19.6 per million population^{1–4}, corresponding to between 3,300 and 6,000 new cases per year in the United States. Following surgical resection, GISTs often recur locally, spread diffusely throughout the serosal surfaces of the abdomen and/or metastasize to the liver. Advanced disease is associated with metastases to distant sites, including to the lung and bone. Prior to the advent of targeted therapies, the prognosis for advanced GISTs was poor owing to their inherent resistance to both chemotherapy and radiation therapy⁵.

During the past decade, GISTs have served as an important model in the emerging field of molecularly targeted therapies for solid tumours. The nearly simultaneous discovery of oncogenic kinase mutations in GISTs and the introduction of kinase inhibitor therapies has led to a rapid evolution in our understanding of these tumours and the biology that defines them.

This Review provides an overview of the exciting developments that have resulted from studies of the molecular pathology, pharmacology and oncology of GISTs. An emphasis is placed on the oncogenic mutations that lead to GIST development, the relationship between these mutations and responses to new classes of targeted therapeutics, and the insights into GIST biology that have been gained from molecular studies.

Oncogenic mutations in GISTs

KIT. As first reported by two groups in 1998, 95% of GISTs are immunohistochemically positive for the receptor

tyrosine kinase *KIT* (also known as CD117), and this remains a crucial diagnostic marker for these tumours. At the same time, Hirota and colleagues published their groundbreaking discovery of *KIT* mutations in GISTs^{6,7}. It is now established that 70–80% of GISTs harbour a *KIT* gene mutation, that these mutations lead to the constitutive activation of the kinase and that mutant *KIT* is a clinically important therapeutic target in GISTs.

KIT is a member of the type III receptor tyrosine kinase family that includes platelet-derived growth factor receptor- α (PDGFRA) and PDGFRB, as well as macrophage colony-stimulating-factor receptor (CSF1R) and Fl cytokine receptor (FLT3)⁸. Binding of the *KIT* ligand, stem cell factor (SCF) to *KIT* results in receptor homodimerization and kinase activation⁹.

Oncogenic *KIT* mutations result in ligand-independent kinase activation (FIG. 1). The most common mutations in *KIT* affect the juxtamembrane domain that is encoded by exon 11. Two-thirds of GISTs harbour mutations in exon 11, which disrupt the normal juxtamembrane secondary structure that prevents the kinase activation loop from swinging into the active conformation¹⁰. These mutations include in-frame deletions, insertions and substitutions, or combinations of these¹¹. The deletions are associated with a shorter progression-free and overall survival in comparison to the other exon 11 mutations^{12–18}. In particular, deletions involving codon 557 and/or codon 558 are associated with malignant behaviour^{19–21}.

Aside from exon 11 mutations, between 7% and 10% of GISTs have a mutation in an extracellular domain that is encoded by exon 9 (REF. 22). These mutations

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At a glance

- Gastrointestinal stromal tumours (GISTs) are a family of tumours thought to arise from the interstitial cells of Cajal in the gastrointestinal tract. Recently, the putative stem and progenitor cells for GISTs have been identified.
- Most GISTs have oncogenic mutations in either KIT or platelet-derived growth factor receptor- α (PDGFRA), and targeting these mutant proteins with kinase inhibitors is effective in patients with advanced disease. There is substantial evidence that these mutations are pathogenetic for the initiation of GISTs.
- GISTs lacking KIT or PDGFRA mutations (known as wild-type GISTs) are a heterogeneous group, of which some have alterations in BRAF, RAS or in the genes of the succinate dehydrogenase complex.
- Classification of GISTs on the basis of molecular defects is relevant to the clinical management of patients. Notably, the response to kinase inhibitor therapy is influenced by the primary kinase genotype.
- Secondary mutations in KIT or PDGFRA eventually lead to drug resistance in most patients.
- A subpopulation of GIST cells with stem cell-like characteristics may be less sensitive to kinase inhibitors, providing the seed for drug resistance.

are thought to mimic the conformational change that the extracellular KIT receptor undergoes when SCF is bound²³. Importantly, the kinase domain in exon 9-mutant KIT is essentially the same as in wild-type KIT, and this has an effect on inhibitor sensitivity. Also important is that these mutations occur in tumours that arise in the small and large intestine, but they are rarely seen in gastric GISTs, and their gene expression profile differs from that of exon 11-mutant tumours²⁴.

Mutations in the activation loop (which is encoded by exon 17) of the kinase are uncommon, and they stabilize the active conformation²⁵. Primary mutations, such as K642E in the ATP-binding region (encoded by exon 13), are also uncommon²⁵. The biological basis of kinase activation by this mutation is unknown, but it is speculated that it interferes with the normal autoinhibitory function of the juxtamembrane domain.

The functional importance of *KIT* mutations in GIST development is supported by several lines of evidence. First, phosphorylated KIT is almost always detectable in GIST tumour extracts²⁶. Second, mutant KIT is oncogenic, supporting the growth of stably transfected BA/F3 cells in nude mice^{6,26}. Third, when expressed in transfected cell lines, mutant forms of KIT show constitutive kinase activity in the absence of SCF, as evidenced by autophosphorylation and the activation of downstream signalling pathways^{6,27,28}. Finally, mice engineered to express KIT with mutations of the type that are found in human GISTs can develop GIST-like tumours^{29,30}. This histological picture is similar to that seen in individuals with inherited KIT-activating mutations^{31,32}.

Tumour extracts from KIT-mutant GISTs demonstrate evidence of activation of downstream signalling pathways, including the MAPK pathway (which consists of RAF, MEK and MAPK), the PI3K–AKT pathway and signal transducer and activator of transcription 3 (STAT3)^{26,33–35} (FIG. 2). The MAPK pathway upregulates important transcriptional regulators such as MYC, ELK and CREB, and can stimulate the cell cycle through FOS. AKT activation through PI3K and 3-phosphoinositide-dependent protein kinase 1 (PDK1)

leads to increased protein translation, downregulation of the cell cycle inhibitor p27 (also known as KIP1) and anti-apoptotic effects.

Recent studies show that ETS translocation variant 1 (ETV1) is an important driver of GIST-specific gene expression during tumorigenesis³⁶. Transduction of an ETV1-targeted short hairpin RNA (shRNA) into GIST cell lines resulted in growth inhibition and apoptosis, and the treatment of GIST cells with either a KIT or a MEK inhibitor markedly reduced ETV1 protein levels through proteasomal degradation. ETV1 transcription is increased by MAPK signalling through the downregulation of the ETS family transcription suppressor capicua (CIC)³⁷. Thus, KIT signalling through the MAPK pathway maintains ETV1 activity.

Pharmacological studies have helped to dissect the relative importance of the pathways downstream of KIT. Despite the finding of ubiquitous MAPK activation in primary GISTs and GIST cell lines, targeted inhibition of MAPK with a MEK1 and MEK2 inhibitor (U0126) had inconsistent effects on GIST cell line proliferation (5–40% inhibition) and did not induce apoptosis. By contrast, PI3K inhibitors had a more marked effect on cellular proliferation (40–75% inhibition) and produced a threefold to fourfold induction in caspase activity. mTOR inhibitors were less effective than PI3K inhibitors for reducing proliferation or for inducing apoptosis, suggesting that the crucial determinants of cell survival signalling are located downstream of PI3K but upstream of mTOR³⁸.

As a negative feedback mechanism, on activation by SCF, signalling from wild-type KIT is quickly downregulated by the endocytic uptake of the receptor from the cell surface, ubiquitylation and proteasome-mediated degradation. In addition to kinase activation, mutant forms of KIT have longer half-lives than wild-type KIT, perhaps partly owing to a stabilizing interaction with heat shock protein 90 (HSP90)^{39,40}.

By immunohistochemistry, KIT is detectable at the surface of GIST cells, but strong staining is commonly observed in the cell cytoplasm and is sometimes concentrated in a perinuclear, dot-like pattern⁴¹. Xiang and colleagues⁴² have observed that KIT with an exon 17 mutation (D816V) is concentrated in the Golgi of transfected A375 cells⁴². Furthermore, mutant KIT that has been further modified with a Golgi-localization motif retains its ability to activate downstream signalling, raising the interesting possibility that signalling from mutant KIT can occur directly from the Golgi.

In general, GISTs are heterozygous for a given mutation; however, in approximately 15% of tumours, the remaining wild-type *KIT* allele is lost, and this allele loss is associated with malignant behaviour^{32,43–45}. In serial samples from individual patients, Chen and colleagues⁴⁵ have provided evidence that this occurs through mitotic non-disjunction, that is, a failure of separation during mitosis of a chromosome 4 pair bearing the wild-type *KIT* allele, thus leaving one daughter cell with a single chromosome 4 bearing the mutant *KIT* allele (this is known as uniparental monosomy). This correlated with increased mitotic activity and topoisomerase II expression⁴⁵.

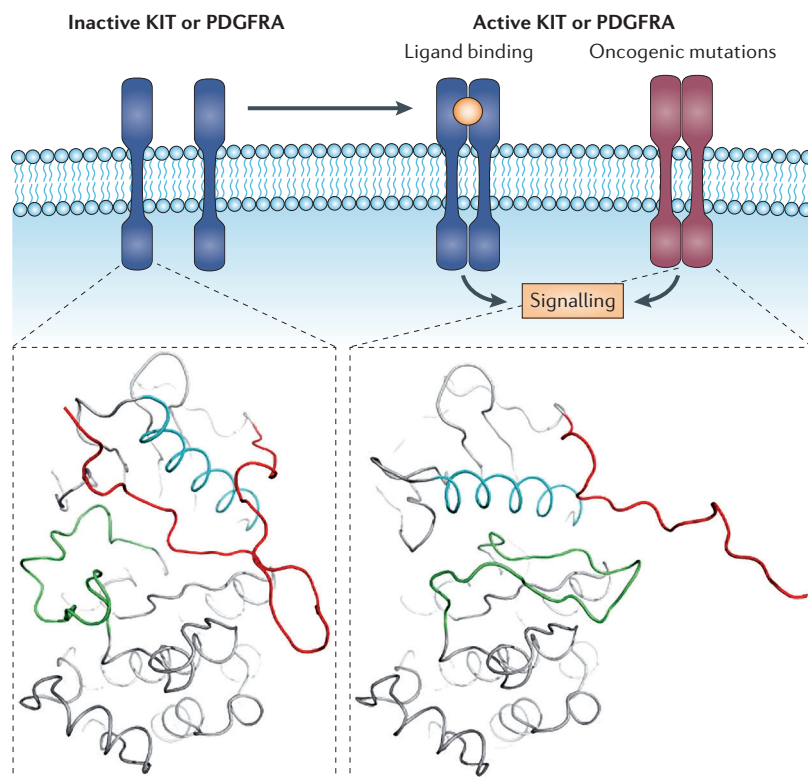


Figure 1 | KIT and PDGFRA structure and mutations. KIT and platelet-derived growth factor receptor- α (PDGFRA) are type III receptor tyrosine kinases and share the same topology: an extracellular ligand-binding domain that is comprised of five immunoglobulin-like repeats, a transmembrane sequence, a juxtamembrane domain and a cytoplasmic kinase domain that is split by an insert; in the case of KIT the insert is 80 amino acids in length. The activation of these receptors occurs through the binding of extracellular ligands that cause receptor dimerization. For KIT, the ligand is stem cell factor (SCF), whereas for PDGFRA, the ligand is PDGFA. Alternatively, oncogenic mutations in these receptors can cause ligand-independent receptor activation. The zoomed panels show the structures of part of the kinase and juxtamembrane domains of inactive KIT (left-hand side) and active KIT (right-hand side). Mutations in the juxtamembrane domain (shown in red), which is encoded by exon 11 of *KIT* or by exon 12 of *PDGFRA*, allow receptor dimerization in the absence of ligand, thus resulting in a conformational change that relieves the suppression of the activation loop (shown in green) of the kinase domain. When the activation loop swings into an open position, the ATP-binding pocket is accessible to ATP, which serves as a phosphate donor for phosphorylation reactions that are catalysed by the kinase. Mutations in the activation loop (encoded by exon 17 of *KIT* or by exon 18 of *PDGFRA*) favour the active conformation of the kinase. Mutations in the extracellular domain of KIT (encoded by exon 9) are also thought to favour receptor dimerization. KIT crystal structures are reproduced, with permission, from REF. 130 © Natl Acad. Sci. USA (2009).

PDGFRA. Of the GISTs that lack *KIT* gene mutations, a minority have high levels of phosphorylation of PDGFRA, as shown by immunoblotting of tumour samples. PDGFRA is a close homologue of KIT⁴⁶, and is activated in GISTs that harbour mutations in the PDGFRA juxtamembrane domain (encoded by exon 12), the ATP-binding domain (encoded by exon 14) or the activation loop (encoded by exon 18) (TABLE 1). Consistent with their extensive functional overlap, *KIT* and *PDGFRA* mutations are mutually exclusive in GISTs^{41,47,48}.

Observations that support the importance of *PDGFRA* mutations in GIST are similar to those for *KIT* mutations. When expressed in transfected cell lines,

mutant forms of PDGFRA have constitutive kinase activity in the absence of their ligand, PDGFA^{46,47}, the activated downstream pathways are identical to those in *KIT*-mutant GISTs^{46,49} and PDGFRA is also stabilized by HSP90 (REF. 50). In addition, both types of tumours are immunopositive for the markers discovered on GIST 1 (DOG1; also known as anoctamin 1) and protein kinase C- θ (PKC θ)^{35,51,52}. These markers are highly selective for GISTs rather than for other mesenchymal tumours. And, as discussed below, both genotypes are associated with cytogenetic changes that are distinctive for GIST^{46,53}.

Despite these molecular similarities, most *PDGFRA*-mutant GISTs show distinctive pathological features from those of *KIT*-mutant GISTs, including differences in gene expression profiles^{49,54}, a striking predilection for the stomach, variable (sometimes negative) expression of KIT^{20,48,51,55–57} and a generally lower potential for malignancy^{58,59}. However, the reasons for these differences are currently unknown.

Other driver mutations. Between 10% and 15% of GISTs do not have a detectable mutation in either *KIT* or *PDGFRA*. In other respects these so-called ‘wild-type’ GISTs are clinically indistinguishable from *KIT*-mutant or *PDGFRA*-mutant GISTs, as they have an identical morphology, express high levels of KIT and occur anywhere in the gastrointestinal tract. Phosphorylated KIT is detectable in these tumours, suggesting that KIT is still activated³⁵, but the mechanism of this activation is unclear. However, recent studies have revealed that wild-type GISTs are a heterogeneous group and display various oncogenic mutations (TABLE 1). For example, the *BRAF* V600E substitution that is common in papillary thyroid carcinoma and melanoma is present in up to 13% of wild-type GISTs⁶⁰. *HRAS* and *NRAS* gene mutations also occur, but are much more rare (M.C.H. and C.L.C., unpublished observations). Because BRAF and the RAS proteins are constituents of the MAPK signalling cascade, they can result in KIT-independent growth stimulation (FIG. 3a), and are possible causes of resistance to KIT and PDGFRA kinase inhibitors.

Defects in the succinate dehydrogenase (SDH) complex of respiratory chain complex II have recently been identified in wild-type GISTs (FIG. 3b). This complex, which is comprised of four subunits (SDHA, SDHB, SDHC and SDHD), oxidizes succinate to fumarate as part of the mitochondrial Krebs cycle. Germline mutations in *SDHB*, *SDHC* or *SDHD* increase the risk not only of the development of GIST, but also of the development of paragangliomas (known as Carney–Stratakis syndrome)⁶¹. Additionally, GISTs have been identified in patients with loss-of-function mutations in *SDHA*⁶². The tumours in affected patients show either loss of or somatic mutation (second hit) of the remaining wild-type allele. Interestingly, some wild-type GISTs lacking an SDH gene mutation show either a marked reduction or an absence of SDHB protein expression by immunohistochemistry, and a corresponding loss of respiratory chain complex II enzymatic activity⁶¹. However, *SDHB*, *SDHC* and *SDHD*

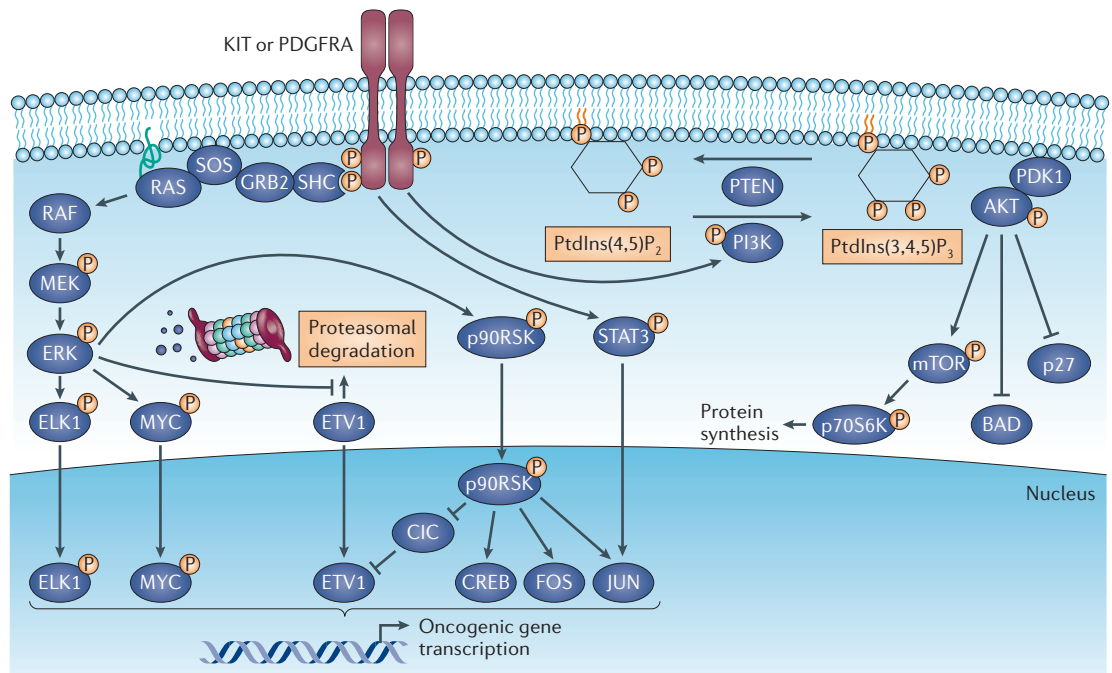


Figure 2 | Oncogenic signalling in KIT and PDGFRA-mutant GISTs. Dimerization of KIT proteins at the cell surface, through the binding of stem cell factor (SCF) or mutational activation, leads to autophosphorylation (P) of tyrosine residues. Phosphotyrosines provide docking sites for a complex of proteins (SHC, GRB2 and SOS) that activates RAS. In turn, RAS activates the MAPK cascade (RAF, MEK and ERK), leading to changes in gene expression through MYC and ELK1. In addition, the activation of p90RSK by ERK leads to the activation of CREB, increased transcriptional activity of FOS and JUN, and the downregulation of capicua (CIC), which is a transcription suppressor of ETS translocation variant 1 (ETV1)^{36,37}. Signal transducer and activator of transcription 3 (STAT3) phosphorylation by KIT also promotes JUN transcription. Proteasomal degradation of ETV1, a crucial developmental regulator of interstitial cells of Cajal (ICCs) and gastrointestinal stromal tumours (GISTs), is regulated by the activity of ERK. Kinase activity of mutated KIT (or of platelet-derived growth factor receptor- α (PDGFRA)) induces the activation of ERK and thereby decreases the degradation of ETV1 in GIST. Finally, activation of PI3K by KIT leads to the conversion of phosphatidylinositol-4,5- bisphosphate (PtdIns(4,5)P₂) to the trisphosphate (PtdIns(3,4,5)P₃) form that allows docking of PDK1 and AKT at the membrane. Phosphorylation of AKT then leads to alterations in protein translation, metabolism and apoptosis through the mediators mTOR and p70S6K. PTEN is a phosphatase (and tumour suppressor) that converts PtdIns(3,4,5)P₃ back to PtdIns(4,5)P₂.

mRNA levels are comparable to those in *KIT*-mutant GISTs, which suggests that SDHB downregulation occurs at the level of protein translation.

The tumorigenic mechanisms of SDH loss-of-function in GISTs remain to be studied, but it is possible that the resulting elevation of succinate levels may negatively regulate prolyl hydroxylase. This enzyme is an important regulator of hypoxia-inducible factor 1 α (HIF1 α) levels, and HIF1 α is a transcriptional activator of insulin-like growth factor 2 (IGF2) and vascular endothelial growth factor (VEGF) (FIG. 3b). In keeping with this model, VEGF expression is higher in wild-type GISTs than in *KIT*-mutant GISTs²⁴. Similar mechanisms have been shown in some types of renal cell carcinoma (through the loss of fumarate hydratase)^{63,64} and in paragangliomas (through mutations in SDH genes).

Approximately 50% of wild-type GISTs show high expression of insulin-like growth factor 1 receptor (IGF1R). Whether this correlates with SDH complex activity remains to be determined, but it is possible that an IGF autocrine loop is sustained in part by loss of SDH and upregulation of IGF2 expression⁶⁵. IGF1R signals through both the MAPK and the PI3K–AKT pathways.

It is estimated that 7% of patients with neurofibromatosis type I (NF1) develop one or more GISTs^{66–70}. Most arise in the small intestine and they do not readily metastasize⁶⁶. The majority of these GISTs are wild-type for *KIT* and *PDGFRA*, but (as expected) they show either somatic mutation or loss of the remaining wild-type neurofibromin 1 (NF1) allele^{66,68,69,71}.

Unlike GISTs in adults, those that arise in paediatric patients (approximately 1–2% of all GISTs) are rarely positive for *KIT* or *PDGFRA* mutations. These tumours, which often metastasize but which tend to grow slowly, have a different gene expression signature from adult-type GISTs^{72–74}. The coexistence of paediatric-type GISTs with pulmonary chondromas and/or paragangliomas in patients, referred to as Carney’s triad, is well described as a non-heritable syndrome⁷⁵. However, the gene or genes for this rare constellation have yet to be identified.

Chromosomal and molecular alterations during GIST progression. Although oncogenic kinase mutations have an important role in the development of GISTs, other genetic events are important in their clinical progression. Approximately two-thirds of GISTs demonstrate

Table 1 | Molecular classification of GISTs

Genetic type	Relative frequency	Anatomic distribution	Germline examples
<i>KIT</i> mutation (relative frequency 75–80%)			
Exon 8	Rare	Small bowel	One kindred
Exon 9 insertion AY502-503	10%	Small bowel and colon	None
Exon 11 (deletions, single nucleotide substitutions and insertions)	67%	All sites	Several kindreds
Exon 13 K642E	1%	All sites	Two kindreds
Exon 17 D820Y, N822K and Y823D	1%	All sites	Five kindreds
<i>PDGFRA</i> mutation (relative frequency 5–8%)			
Exon 12 (such as V561D)	1%	All sites	Two kindreds
Exon 14 N659K	<1%	Stomach	None
Exon 18 D842V	5%	Stomach, mesentery and omentum	None
Exon 18 (such as deletion of amino acids IMHD 842–846)	1%	All sites	One kindred
<i>KIT</i> and <i>PDGFRA</i> wild-type (relative frequency 12–15%)			
<i>BRAF</i> V600E	~7–15%		
<i>SDHA</i> , <i>SDHB</i> , <i>SDHC</i> and <i>SDHD</i> mutations	~2%	Stomach and small bowel	Carney–Stratakis
<i>HRAS</i> and <i>NRAS</i> mutation	<1%		
Sporadic paediatric GISTs	~1%	Stomach	Not heritable
GISTs as part of the Carney triad	~1%	Stomach	Not heritable
NF1-related	Rare	Small bowel	Numerous

GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type I; *PDGFRA*, platelet-derived growth factor receptor- α ; SDH, succinate dehydrogenase.

either monosomy of chromosome 14, or partial loss of 14q^{46,76–80}. Interestingly, these chromosome 14 abnormalities are observed both in *KIT*-mutant and in *PDGFRA*-mutant GISTs^{46,53}. Based on loss of heterozygosity (LOH) and comparative genomic hybridization (CGH) studies, there are two regions of this chromosome that may harbour tumour suppressor genes that are important in early GIST formation^{77,81}. Deletions of 14q11.2 include the genes *PARP2*, *APEX1* and *NDRG2*, and deletions of 14q32 include the *SIVA* gene⁸². Loss of the long arm of chromosome 22 is observed in approximately 50% of GISTs^{46,53,76,77,80,83}.

Losses on chromosomes 1p, 9p, 11p and 17p are successively less common than 14q and 22q losses, but are more significantly associated with malignancy^{46,53,76,80,83–86}. Losses on chromosomes 10, 13q and 15q have also been reported in GISTs^{53,83,87}. Gains on chromosomes 8q (including *MYC*), 3q (including *SMARCA3*) and 17q are associated with metastatic behaviour^{77,81,87,88}. In a recent array-based analysis of gene copy number in 42 GISTs (23 with recurrence or metastasis), the tumours were separated into four groups that reflected their accumulated chromosomal changes. The overall survival of group 1 (loss of 22q, 19 and 1p distal) and group 2 (additional loss of 14q) was significantly better than that of group 3 (additional losses of 15q and 1p proximal) and group 4 (additional loss of 10). This indicates that the accumulation of chromosomal lesions generally indicates a worse prognosis. Specific genes that were implicated in this analysis included *OXA1L* on 14q, as well as *AKAP13* and *C15orf5*

on 15q⁸⁷. Chibon *et al.*⁸⁹ have generated a gene expression profile that correlates with chromosomal instability in sarcoma. Use of the chromosomal instability gene signature allowed the classification of GISTs into populations with a low or a high propensity to develop metastatic disease⁸⁹.

None of the above karyotypic changes is present in paediatric-type GISTs, which remain near-diploid, again emphasizing the different biology of these tumours⁷⁴. By contrast, GISTs arising in patients with NF1 often show losses of 14q and 22q⁹⁰.

On the basis of gene expression profiling of high-risk versus low-risk GISTs, the high-risk tumours show significant changes in genes that regulate the cell cycle, including genes that are influenced by the PI3K pathway and genes that are involved in the G2/M cell cycle checkpoint⁹¹. A considerable proportion of malignant GISTs show inactivation of the tumour suppressor gene *CDKN2A* (which encodes the cell cycle regulatory proteins INK4A and ARF) through chromosome 9p21 deletion, either biallelic or in combination with mutation or promoter methylation^{92–96}. Methylthioadenosine phosphorylase (*MTAP*) is just telomeric to *CDKN2A* and can be co-deleted in high risk and malignant GISTs, resulting in a defect in the adenosine salvage pathway⁹⁷. Another cell cycle inhibitor, p27, is also commonly downregulated in malignant GISTs, but the association with tumour progression is not as well supported as that for INK4A^{95,98,99}. Increased expression levels of cyclin A and cyclin H are associated with high-risk GISTs^{97,98,100}. *TP53* mutations and decreased p53 immunostaining also correlate

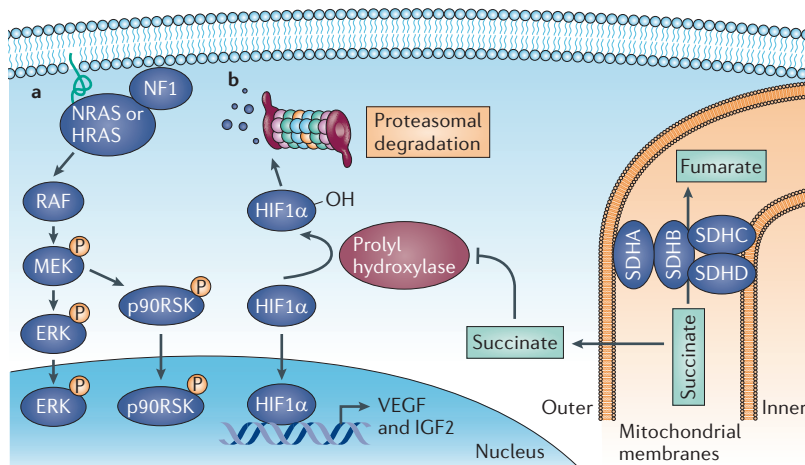


Figure 3 | Oncogenic signalling in wild-type GISTs. Mutations in neurofibromin 1 (NF1), RAS or BRAF can all increase signalling through the MAPK cascade (part a), leading to changes in gene expression (FIG 2). The succinate dehydrogenase (SDH) complex is comprised of four subunits (part b), two of which (SDHC and SDHD) are anchored in the inner mitochondrial membrane. SDHA and SDHB coordinate the oxidation of succinate to fumarate as part of the Krebs' cycle. Loss of SDH complex activity owing to mutational inactivation of any of the SDH subunits leads to the cytoplasmic accumulation of succinate, which downregulates prolyl hydroxylase. This enzyme is an important negative regulator of hypoxia-inducible factor 1 α (HIF1 α): by hydroxylating HIF1 α , prolyl hydroxylase promotes the proteasomal degradation of HIF1 α . Therefore, increased succinate levels lead to increased levels of HIF1 α , which can enter the nucleus and activate the transcription of vascular endothelial growth factor (VEGF) and insulin-like growth factor 2 (IGF2). GISTs, gastrointestinal stromal tumours.

with a poor prognosis^{101–103}. Likewise, amplifications of *MDM2* and *CCND1* (which encodes cyclin D1), though uncommon in GISTs, are associated with malignancy¹⁰⁴. Whether microRNA (miRNA) dysregulation plays a part in GIST development remains unclear, but miR-221 and miR-222 levels are significantly lower in KIT-expressing GISTs than in KIT-negative GISTs¹⁰⁵.

The origin of GISTs

Interstitial cells of Cajal. During the 1990s a number of investigators noted similarities between GISTs and a population of cells in the gastrointestinal tract called the interstitial cells of Cajal (ICCs), which are pacemakers for peristaltic contractions. These observations led to the hypothesis that ICCs could be the cell-of-origin of GISTs. Mice that are engineered to express KIT with mutations of the type found in human GISTs develop diffuse ICC hyperplasia in the muscular wall of the stomach and intestine^{29,30}. As mentioned above, these mice also develop GIST-like tumours. In a strain expressing KIT^{K641E}, the numbers of ICC stem cells (KIT^{low} CD44⁺ CD34⁺) and mature myenteric ICCs were increased, indicating that the mutant KIT can cause expansion of ICCs¹⁰⁶. Diffuse ICC hyperplasia has been described in several kindreds with heritable mutations in *KIT* (TABLE 1), and is associated with dysphagia and the development of multiple GISTs^{29,32,35,67,107–112}, although many of the tumours do not follow a malignant course.

The relationship between GISTs and ICCs is further supported by parallels in gene expression. For example, high levels of PKC θ , nestin and DOG1 are expressed in

both GISTs and ICC cells^{113–119}. In addition, the ETS family transcription factor ETV1 is highly expressed in both GISTs and the specific subpopulations of ICCs (myenteric and intramuscular, as opposed to submucosal) that are thought to give rise to GISTs³⁶.

The observation that some *KIT* and *PDGFRA* mutations in GISTs correlate closely with anatomical location (TABLE 1) might be explained by their ICC origin^{24,49,54}. For example, GISTs with a *KIT* exon 9 mutation, which primarily arise in the intestines, may derive from a different subgroup of ICCs than those with a *PDGFRA* D842V mutation, which occur only in the stomach, mesentery and omentum^{58,120,121}. The more common *KIT* mutations, by contrast, can be found in GISTs throughout the gastrointestinal tract, perhaps deriving from a more ubiquitous ICC subtype.

Micro-GISTs. Minute growths (1–10 mm in size) of cells that are similar to ICCs and GISTs are present in between 2.9% and 35% of stomachs that are thoroughly examined after surgical removal or at autopsy^{122–125}. These ‘micro-GISTs’ are mitotically inactive and often partially calcified, suggesting tumorigenic arrest. In contrast to the diffuse ICC hyperplasia that is observed in the presence of a germline *KIT* mutation, micro-GISTs appear to represent a nodular form of ICC overgrowth that is caused by local, somatic acquisition of a *KIT* mutation. The type and frequency of *KIT* mutations in micro-GISTs is essentially the same as in clinically relevant tumours¹²⁶, including lesions with deletions affecting codon 557 and codon 558. Sub-centimetre GISTs with *PDGFRA* mutations have also been reported¹²². These observations on micro-GISTs suggest that kinase gene mutations occur very early in GIST tumorigenesis; however, these mutations are probably not sufficient for progression to an oncologically threatening lesion. The large pool of micro-GISTs in the general population probably explains the multiple reported cases in which two or more genotypically distinct GISTs are found in a patient during a single surgical procedure^{67,122,127,128}.

Kinase mutations and TKI therapy

Until the year 2000, treatment options for patients with advanced GIST were poor. The response rate to conventional chemotherapy was <5% and median survival for patients with advanced disease was approximately 18 months⁵.

The tyrosine kinase inhibitor (TKI) imatinib was developed in the early 1990s as a therapy for chronic myelogenous leukaemia (CML) owing to its ability to inhibit the fusion oncoprotein BCR–ABL¹²⁹. The observation that ABL shares structural similarity with KIT and several other tyrosine kinases led to experiments showing that imatinib can inhibit the growth of cells that express activated KIT-mutant isoforms²⁷. In addition, imatinib showed potent activity against a KIT-mutant GIST cell line²⁸. Imatinib inhibits KIT by directly binding to the ATP-binding site within the amino-terminal lobe of the kinase and so competitively inhibiting ATP binding. The KIT receptor is normally in equilibrium between active and inactive conformations. The inactive conformation is favoured by steric hindrance that is conferred

Dysphagia

Difficulty swallowing.

Myenteric

Referring to the gastrointestinal tract.

Mesentery

The membranous support for blood vessels serving the gastrointestinal tract.

Omentum

A fatty membrane attached to the stomach and covering the anterior abdomen.

Cross-over

Switching from one arm of a trial to the other.

by the juxtamembrane domain, which prevents the activation loop from assuming the conformation that is required for kinase activation. In this inactive state, imatinib binds to the amino acids Cys673 in the hinge region, Glu640 in the proximal kinase domain, and Asp810 and Phe811 in the DFG motif between the proximal and distal kinase domains. Imatinib stabilizes the kinase in the inactive conformation^{10,130,131}.

With the knowledge that imatinib inhibits KIT signalling, imatinib was first used clinically to treat a 50-year-old female with metastatic GIST, and a dramatic response was seen¹³². Following promising results from Phase I and Phase II trials, two international Phase III trials were launched, with each using similar protocols to allow a subsequent meta-analysis. The Phase III trials compared treatment with 400 mg daily and treatment with 800 mg daily of imatinib, and these trials had cross-over. Overall, imatinib achieved disease control in 70–85% of patients with advanced KIT-positive GISTs, and the median progression-free survival was 20–24 months^{133–137}. Currently, the median survival for patients with advanced disease who are treated with front-line imatinib is 5 years, with 34% of patients surviving more than 9 years¹³⁸. More recently, adjuvant imatinib treatment has been shown to decrease the risk of relapse after curative intent surgery¹³⁹.

Responses to TKI therapy

Clinical disease persistence. Clinical data suggest that even long-term TKI treatment fails to eradicate GIST cells, resulting in disease persistence. In an attempt to determine the optimal duration of imatinib therapy for advanced or unresectable GIST, one interesting trial randomized patients who had continuous control of their disease after 3 years of imatinib treatment to either continue or to discontinue treatment¹⁴⁰. The 2-year progression-free survival rate was 80% in the continuous treatment cohort and only 16% in the interruption group. Patients who relapsed after the discontinuation of therapy did so because of persistent disease (that is, the failure of imatinib to eradicate GIST cells). By contrast, the progression that developed in some of the patients who continued therapy was due to resistant disease.

Theoretically, the persistence of GIST cells during TKI treatment could be due to the failure of these drugs to eradicate mature GIST cells and/or GIST stem cells (BOX 1). Current evidence suggests that both mechanisms underlie GIST persistence in the face of prolonged TKI therapy^{106,141}.

Given the above results, it is not surprising that most GIST lesions that are treated with a TKI still harbour viable cells. For example, Agaram and colleagues¹⁴²

Box 1 | GIST stem cells

Bardsley *et al.*¹⁰⁶ have recently identified a mouse gastrointestinal stromal tumour (GIST) stem cell with a KIT^{low} CD44⁺ CD34⁺ insulin-like growth factor 1 receptor (IGF1R)⁺ immunophenotype. Immature interstitial cells of Cajal (ICCs) in their model system are KIT⁺ CD44⁺ CD34⁺ IGF1R⁺, whereas differentiated GIST cells are KIT⁺ CD44⁻ CD34⁻ IGF1R⁻. These investigators found that the GIST stem cell and immature ICC populations are largely resistant to genetic or pharmacological inhibition of KIT signalling, whereas the proliferation of GIST differentiated cells was completely dependent on functional KIT activity¹⁰⁶.

Property	ICC stem cell population	Immature ICC population	Differentiated ICC population
Phenotype ¹⁰⁶	KIT ^{low} CD44 ⁺ CD34 ⁺ IGF1R ⁺	KIT ⁺ CD44 ⁺ CD34 ⁺ IGF1R ⁺	KIT ⁺ CD44 ⁻ CD34 ⁻ IGF1R ⁻
ETV1 expression ³⁶	Yes	• Yes: ICC-MY* and ICC-IM [‡] • No: ICC-SMP [§] and ICC-DMP	• Yes: ICC-MY and ICC-IM • No: ICC-SMP and ICC-DMP
Effect of germline KIT-activating mutation ¹⁰⁶	Increased	• Increased: ICC-MY and ICC-IM • No change: ICC-SMP and ICC-DMP	• Increased: ICC-MY and ICC-IM • No change: ICC-SMP and ICC-DMP
Effect of germline inactivating KIT mutations ¹⁰⁶	No change	No change	Decreased
Effect of germline mutation reducing membrane-bound KIT ligand expression ¹⁰⁶	No change	Decreased	Decreased
Effect of imatinib on proliferation ¹⁰⁶	None	None	Decreased
Effect of neutralizing KIT or KIT ligand antibody ¹⁰⁶	None	Not reported	Decreased

ETV1, ETS translocation variant 1; ICC-DMP, ICC-deep muscular plexus; ICC-IM, ICC-intramuscular; ICC-MY, ICC-myenteric; ICC-SMP, ICC-submucosal plexus. *ICC-MY cells form a network of ICCs between the circular muscle and the longitudinal muscle layers surrounding the neuronal myenteric plexus. Present in stomach, large and small intestines. These cells express ETV1 and can give rise to GISTs. [‡]ICC-IM cells are singly dispersed ICCs in the circular muscle. Present in the stomach, large and small intestines. Also referred to as ICC-circular muscle (ICC-CM) in the stomach and large intestine. These cells express ETV1 and can give rise to GISTs. [§]ICC-SMP cells form an ICC network surrounding the submucosal plexus. Present in the large but not the small intestine. Similar network known as ICC-submucosa (ICC-SM) are present in the pylorus of the stomach. These cells do not express ETV1 and do not give rise to GISTs. ^{||}ICC-DMP cells form an ICC network around the deep muscular plexus in the circular muscle close to the muscosa. Present in the small intestine but not the stomach or large intestine. These cells do not express ETV1 and do not give rise to GISTs^{36,191}.

examined a series of 43 clinically responsive GIST lesions from 28 patients. Histological responses in these resected tumours after 1 to 31 months of imatinib treatment ranged from a <10% to a >90% reduction in tumour cellularity. In most cases, these lesions have little or no metabolic activity (discussed below) and appear on computed tomography (CT) scans as cystic remnants of a larger mass, thus suggesting a completely treated tumour. Surprisingly, few lesions showed a complete loss of tumour cells and overall responses did not correlate with the mutational status of *KIT* or *PDGFRA*, nor with the duration of treatment. However, the residual tumour cells in 75% of the lesions were quiescent, as judged by an absence of mitoses and a proliferative index of 0% by Ki-67 staining. Interestingly, some tumour cells showed transdifferentiation towards a smooth muscle phenotype, as evidenced by immunohistochemistry, electron microscopy and gene expression analyses. Thus, under imatinib suppression, GIST cells may avoid apoptosis by exiting the cell cycle and by expressing genes that are associated with a differentiated phenotype.

Metabolic changes. Functional imaging of GIST metabolism by F18-fluorodeoxyglucose (F18-FDG) positron emission tomography (PET) carried out within 24 hours of the first dose of imatinib showed a significant decrease in FDG signal in tumours that had a robust response to imatinib¹⁴³. This *in vivo* evidence suggests that one of the initial effects of kinase inhibition in GISTs is a decrease in glycolytic metabolism. On follow-up CT scans, many patients have objective tumour responses, but other patients have little or no change in overall tumour bulk. Only a small minority of patients (3–5%) that are treated with imatinib show a complete disappearance of their disease^{135,144–146}. Regardless, it is now established that patients with tumours that remain stable in size have the same clinical benefit as patients with tumour shrinkage¹⁴⁷.

Responses in experimental systems. The above clinical results are mirrored by cellular models of imatinib-sensitive GIST. These *KIT*-mutant GIST cell lines derived from human tumour specimens typically retain substantial sensitivity to the inhibitory effects of imatinib on *KIT* kinase activity, unless they are subjected to carcinogen-induced mutagenesis. Imatinib treatment of these cell lines induces a strong anti-proliferative effect, leading some cells to go undergo apoptosis through a mechanism that is dependent on histone H2AX, highlighting the requirement of these cells for oncogenic *KIT* signalling, a phenomenon that is often referred to as oncogene addiction^{148,149}. However, many cells simply become quiescent through nuclear p27-mediated exit from the cell cycle, as well as by upregulation of autophagy. Even after prolonged exposure, the removal of imatinib from the culture system allows the cells to resume proliferation^{141,148}.

It is possible, however, to induce apoptosis in quiescent GIST cells by using imatinib-synergistic treatments such as ABT-737 (a BCL-2 inhibitor) or RNA interference directed against the pro-apoptotic BCL-2 family member, *BIM*^{150,151}. In addition, inhibition of

the autophagy survival pathway by small interfering (siRNA) against *ATG7* or *ATG12*, or chloroquine inhibition of lysosomal acidification, can also induce apoptosis in GIST cells that are quiescent during imatinib treatment¹⁴¹. These data suggest that some form of combination therapy might improve the ability of current TKIs to kill GIST cells.

There is also emerging evidence that GIST stem cells are inherently resistant to *KIT* inhibitors (BOX 1). In the stem cell population of a mouse model of GIST, IGF1R was identified as an alternative regulator of cellular proliferation and survival. *KIT* mutations seem to confer a competitive growth advantage to GIST stem cells over non-transformed ICC stem cells, but the growth and survival of these cells is not completely dependent on *KIT* signalling. Therefore, TKI therapy can control the growth and survival of differentiated GIST cells that account for most of the cellular composition of clinical GIST lesions, but this therapy may not control or eradicate the GIST stem cell and progenitor cell pool¹⁰⁶.

Resistance to TKI therapy

Primary resistance. Resistance to treatment with *KIT* and *PDGFRA* inhibitors such as imatinib can be divided into two types: primary and secondary. Approximately 10% of patients with GISTs have primary resistance, which is defined as progression within the first 6 months of treatment. One of the interesting observations that has emerged from the Phase II trials, and which was confirmed in the Phase III trials, is that tumour response to imatinib correlates with the underlying kinase genotype^{43,51,137,146,152}. The probability of primary resistance to imatinib for *KIT* exon 11, *KIT* exon 9 and wild-type GISTs is 5%, 16% and 23%, respectively⁴³.

Despite the poor clinical prognosis of exon 11-mutant *KIT* GISTs in the absence of imatinib treatment, this mutant is highly sensitive to imatinib *in vitro*, with a half-maximal inhibitory concentration (IC_{50}) of <100 nM, and exon 9-mutant *KIT* and wild-type *KIT* are less sensitive to the drug (with an IC_{50} of ~1,000 nM for each)¹⁵³. Thus, underdosing of imatinib in patients with exon 9 mutations probably accounts for some of the apparent resistance¹³⁷. Correspondingly, patients with a tumour harbouring exon 11 mutations have a significantly better progression-free and overall survival than patients with a tumour that has an exon 9 mutation or no detectable *KIT* or *PDGFRA* mutation^{137,146,152}. These outcomes correlate with the above rates of primary resistance from these GIST genotypes.

Based on *in vitro* data, the most common *PDGFRA* mutation in GISTs, D842V, is strongly resistant to the effects of imatinib^{43,47,154,155}. This mutation favours the active conformation of the kinase domain and consequently disfavours imatinib binding^{43,130,156}. This has been corroborated by clinical results, as patients with *PDGFRA* D842V-mutant GIST have low response rates and very short progression-free survival and overall survival during imatinib treatment. There are, however, some *PDGFRA* mutants that are sensitive to imatinib *in vitro*, and patients with these mutations have shown durable responses to imatinib.

Wild-type GISTs include tumours with mutations downstream of KIT^{60,61,157,158}, hence these subsets of wild-type GISTs might respond better to other targeted agents, such as VEGFR inhibitors for paediatric or SDH-mutant GIST, and BRAF or MEK inhibitors for BRAF-mutant GIST¹⁵⁹.

Secondary resistance. After an initial benefit from imatinib, the vast majority of patients eventually develop disease progression or secondary resistance. The resistance may manifest in a number of ways, including growth of a nodule within a pre-existing, clinically quiescent lesion, the development of one or more new nodules, or widespread expansion of lesions throughout the liver or abdominal cavity. It is now established that acquired mutations in *KIT* or *PDGFRA* account for most secondary resistance, and that these mutations occur almost exclusively in the same gene and allele as the primary oncogenic driver mutation^{44,160–166}.

In a Phase II imatinib study for advanced GISTs, 67% of the patients whose tumour showed imatinib resistance had a new, or secondary, mutation in *KIT*. Notably, these mutations were common among tumours with a primary exon 11 mutation, but were not observed in wild-type GIST samples¹⁶³. Secondary mutations of *KIT* have not been reported in wild-type GISTs, suggesting that *KIT* activation is not the primary driver of tumour growth in these cases. Unlike primary mutations that activate *KIT*, which are predominantly in the juxtamembrane regions that are encoded by exons 9 and 11, the secondary mutations were concentrated in two regions of the *KIT* kinase domain, which is the domain that is targeted by imatinib (FIG. 4). One is the ATP-binding pocket, encoded by exons 13 and 14, mutations of which directly interfere with drug binding. The second is the activation loop, where mutations can stabilize *KIT* in the active conformation and thereby hinder drug interaction. Compounding the problem, almost all of the secondary exon 17 or 18 *KIT* mutations can also serve as primary activation mutations, thus potentially increasing kinase activity. By contrast,

the secondary ATP-binding pocket mutations do not cause intrinsic kinase activation^{44,142,163,167–169}. Drug resistance has also been observed in *PDGFRA*-mutant GISTs, in which the most common is an acquired D842V mutation (activation loop)^{161,163}. However, there have been no reliable reports of a secondary *KIT* mutation arising in a GIST with a primary *PDGFRA* mutation, or vice versa, during treatment with imatinib.

Additional studies using more sensitive assays have identified secondary mutations in more than 80% of drug-resistant GIST lesions^{169–172}. More sobering is that there is a considerable heterogeneity of resistance across different lesions, and even within different areas of the same lesion^{44,163,168,173}. For example, there have been reports of up to five different drug resistance mutations in different portions of an individual lesion and of up to seven different secondary resistance mutations across multiple tumours in the same patient^{169,172}. This heterogeneity of resistance substantially affects the efficacy of salvage TKI therapy after front-line imatinib treatment because the diversity of resistant, minority clones precludes the systemic eradication of GIST cells by any particular TKI.

Although secondary mutations in *KIT* are the most common cause of acquired resistance to imatinib therapy, there are other potential causes for GIST growth in the face of TKI therapy. For example, there can be down-regulation or loss of *KIT* and *PKCθ* expression, which is associated with a marked increase in cyclin D1 and *JUN* levels¹⁷⁴. Overexpression of *IGF1R* has been shown in GISTs lacking primary *KIT* or *PDGFRA* mutations, and the inhibition of *IGF1R* may kill GIST cells independently of *KIT* mutational status^{65,175}. Focal adhesion kinase (*FAK*) may also have a role in the growth and survival of imatinib-resistant GIST cells¹⁷⁶. In addition, an imatinib-resistant GIST cell line and two patients with *KIT*-negative GISTs were observed to have overexpression of the tyrosine kinase *AXL*, which activates similar pathways to *KIT*¹⁷⁷.

Approaches to imatinib-resistant GISTs

Prior to switching therapy in patients with progression on imatinib, it is recommended that the dose of imatinib is increased. Although the median time to progression following dose escalation is only 5 months, a small proportion of all patients with GISTs (20–30%) may have prolonged disease control lasting 1 year or more¹³⁵. Presumably, such responses are due to either inadequate drug concentrations that are boosted following dose escalation and/or the achievement of higher drug concentrations that are able to biochemically inhibit some secondary mutations that are associated with relative rather than absolute imatinib resistance.

Alternative TKIs that target KIT and PDGFRA.

Unfortunately, most patients will not respond to imatinib dose escalation, forcing a switch to an alternative *KIT* and *PDGFRA* TKI. Such salvage agents include sunitinib, sorafenib, vatalanib, masitinib, nilotinib and dasatinib, as well as other investigational inhibitors (TABLE 2). Although all of these agents are *KIT* and *PDGFRA* inhibitors,

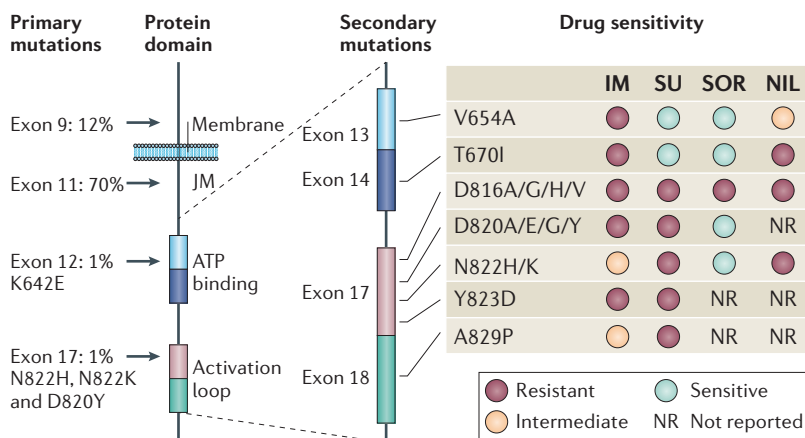


Figure 4 | **Secondary mutations in *KIT* and their drug sensitivities.** A comparison of the relative *in vitro* potency of imatinib (IM), sunitinib (SU), sorafenib (SOR) and nilotinib (NIL) versus secondary mutations that are associated with resistance to imatinib, as assessed by *in vitro* expression studies^{153,163,192–194}, is shown. JM, juxtamembrane. Figure is modified, with permission, from REF. 130 © Natl Acad. Sci. USA (2009).

Table 2 | **New therapies being tested for the treatment of GISTs**

Drug	Targets	Trial information
Tyrosine kinase inhibitors		
Imatinib	KIT and PDGFRA	FDA approved
Sunitinib	KIT, PDGFRA and VEGFR	FDA approved
Nilotinib	KIT and PDGFRA	Phase III (ClinicalTrials.gov ID: NCT00785785)
Dasatanib	KIT and PDGFRA	Phase II (NCT00568750)
Sorafenib	KIT, PDGFRA and VEGFR	Phase II (NCT01091207)
Regorafenib	KIT, PDGFRA and VEGFR	Phase III (NCT01271712)
Vatalanib	KIT, PDGFRA and VEGFR	Phase II (NCT00117299)
Masitinib (AB1010)	KIT and PDGFRA	Phase III (NCT00812240)
Pazopanib	KIT, PDGFRA and VEGFR	Phase II (NCT01323400)
Crenolanib	PDGFRA	Phase II (NCT01243346)
HSP90 inhibitors		
STA-9090	HSP90	Phase II (NCT01039519)
AT-13387	HSP90	Phase II (NCT01294202)
AUY922	HSP90	Phase II (NCT01404650)
Monoclonal antibodies		
IMC-3G3 (Olaratumab)	PDGFRA	Phase II (NCT01316263)
Bevacizumab	VEGFR	Phase III (NCT00324987)
mTOR inhibitor		
Everolimus	mTOR	Phase II (NCT00510354)
Other		
Perifosine	AKT (PI3K pathway)	Phase II (NCT00455559)

FDA, US Food and Drug Administration; GISTs, gastrointestinal stromal tumours; HSP90, heat shock protein 90; PDGFRA, platelet-derived growth factor receptor- α ; VEGFR, vascular endothelial growth factor receptor.

most of them (in contrast to imatinib) also target VEGFR1 and VEGFR2 (REF. 178), hence these agents have the potential to decrease tumour growth by the inhibition of angiogenesis, as well as by the direct inhibition of KIT and PDGFRA. It remains unclear, however, whether the additional VEGFR1 and VEGFR2 inhibition contributes to disease stabilization that can be seen on treatment of imatinib-resistant GIST with salvage agents.

Sunitinib is US Food and Drug Administration (FDA)-approved for the treatment of patients with GISTs with progression on imatinib¹⁷⁹ but biochemical evidence suggests that the range of activity of sunitinib against secondary imatinib-resistant kinase mutations is suboptimal. Although KIT ATP-binding pocket mutations are extremely sensitive to sunitinib *in vitro*, the activation loop mutations are strongly cross-resistant to sunitinib (FIG. 4). Given the approximately equal frequency of these different classes of mutations in imatinib-resistant lesions and the multiplicity of lesions in a typical patient, it is not surprising that mixed responses are common during sunitinib therapy^{146,180}. One interesting example of serial mutations is a case reported by Nishida *et al.*¹⁸⁰ in which an imatinib-resistant tumour that had a primary exon 11 mutation and a secondary exon 13 mutation, acquired (in *cis*) a tertiary activation loop mutation during sunitinib treatment.

Nilotinib is a drug that is structurally similar to imatinib and that has limited activity against ATP-binding pocket mutations and activation loop mutations (FIG. 4) and that therefore displays minimal efficacy in imatinib-resistant cells. By contrast, *in vitro* studies suggest that sorafenib has broader activity than nilotinib (and sunitinib) against imatinib-resistance mutations (FIG. 4). Correspondingly, nilotinib has shown limited activity in patients with imatinib-resistant GISTs in Phase II clinical trials, whereas a sorafenib analogue (regorafenib) provided a remarkable 10-month median progression-free survival, prompting a Phase III trial that is currently underway^{181–183}.

Even with newer drugs such as regorafenib, resistance develops over time, suggesting that escape from ATP-competitive inhibitors of KIT and PDGFRA is inevitable. Interestingly, a new class of non-ATP mimetic kinase inhibitors (known as switch pocket kinase inhibitors, such as DP-2976) have shown high potency when tested *in vitro* against imatinib-resistant KIT mutants^{184,185}. This class of drugs, which suppresses the conformational switch to the activated form of KIT, represents a novel alternative in the battle against TKI resistance.

Other agents. There is evidence that the PI3K–mTOR signalling pathway is one of the most important pathways in the growth of GIST cells³⁸, and multiple medications targeting this pathway are in clinical development. Testing these agents in isolation or in combination with potent KIT inhibitors is a logical next step in developing better treatments for drug-resistant GIST. There are also ongoing efforts to test HSP90 inhibitors in the treatment of TKI-resistant GISTs (TABLE 2). This class of compounds has been shown to have *in vitro* activity against imatinib-resistant GISTs, but not as much activity in wild-type or primary KIT-mutant GISTs³⁹.

Given that multiple secondary mutations frequently develop during monotherapy with a kinase inhibitor, it is time to consider treatment approaches that use multiple agents. In theory, an inhibitor ‘cocktail’ could not only prevent secondary resistance from emerging, but might also knock out GIST stem cells and thereby eradicate the disease. However, it can be challenging to combine small-molecule inhibitors for simultaneous treatment, as many of these drugs are metabolized by shared cytochrome P450 pathways (for example, CYP3A4). In particular, combining drugs that inhibit or that induce pathways that are responsible for the metabolism of a co-administered drug can be difficult, if not impossible^{186,187}.

Conclusions and future directions

Achievements in the treatment of GISTs during the past decade are the direct result of a growing understanding of their molecular biology. Although the current recommendations for assessing the risk of progression of a newly diagnosed primary GIST are based on three simple parameters: tumour size, tumour location and mitotic index (mitoses per 5 mm²)^{188–190}, the accuracy of prognoses is likely to be enhanced by incorporating the mutational status of GISTs.

The high frequency of primary KIT and PDGFRA mutations in these tumours makes them sensitive to kinase inhibitors such as imatinib, but resistance develops in most cases. An immediate research goal is to develop new inhibitors that can inhibit secondary activation loop mutations that confer cross-resistance to all clinically available TKIs. In addition, the development of effective combination therapy is likely to improve tumour control. To date, our therapeutic approach to GISTs is focused on gain-of-function kinase mutations, but ongoing high-throughput genomic studies are likely to identify additional drivers and modifiers of GIST biology that can be targeted.

The clinical utility of GIST mutational status is highlighted by the finding that *KIT* exon 9-mutant GISTs require a higher dose of imatinib for optimal disease

control. In addition, certain molecular subtypes of GISTs are less effectively treated by conventional KIT inhibitors, but may be better treated with agents that target the underlying biology (for example, SDH-deficient GISTs and PDGFRA D842V GISTs). In addition to the use of tumour genotype to individualize treatment, future improvements in molecular imaging may allow further treatment optimization.

In summary, new insights into the origin and progression of GISTs are setting the stage for further therapeutic innovations, with the goal not only of controlling disease growth, but also of eliminating all tumour cells at the time of initial therapy. Thus, the current challenge from GISTs is to move from a paradigm of tumour suppression to one of free cancer cure.

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Competing interests statement

C.L.C. and M.C.H. declare [competing financial interests](#). See Web version for details.

FURTHER INFORMATION

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