Inhibition of oncogenic and drug-resistant PDGFRA and KIT alterations by DCC-2618

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Introduction

Activating mutations and other genetic alterations in KIT and PDGFRA receptor tyrosine kinases have been identified in certain cancers and proliferative diseases, including >85% of cases of gastrointestinal stromal tumors (GIST), >90% of systemic mastocytosis (SM), and small percentages of gliomas, lung cancer, melanomas, and leukemias. The treatment of metastatic GIST has been transformed with KIT inhibitors, but heterogeneous drug-resistant mutations arise during therapy, with individual patients often having multiple KIT mutations in different tumor sites. PDGFRA variants in GIST and other cancers also have a significant unmet medical need. DCC-2618 is a kinase switch control inhibitor that potently and broadly inhibits primary and drug-resistant KIT mutations in exons 9, 11, 13, 14, 17 and 18, as well as primary PDGFRA mutations in exons 12, 14, and 18. DCC-2618 has been designed to bind as a type II switch control kinase inhibitor that forces the mutant kinases, including strongly activated mutants such as D816V KIT and D842V PDGFRA, into inactive conformations. DCC-2618 has been observed to be potent in enzyme and cell-based assays, and has demonstrated consistent efficacy in xenograft models driven by PDGFRA or KIT alterations. Based on this profile, DCC-2618 may have utility in the treatment of KIT and PDGFRA-driven cancers including GIST and SM. DCC-2618 is currently in a Phase 1 clinical trial in KIT and PDGFRA-driven cancers (ClinicalTrials.gov Identifier: NCT02571036) and a Phase 3 clinical trial in GIST patients who have progressed on or are intolerant to imatinib, sunitinib, and regorafenib (ClinicalTrials.gov Identifier: NCT03353753).

DCC-2618 Structure and Type-II Binding Mode

Figure 1

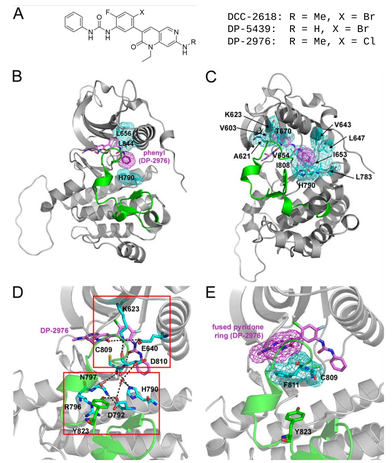
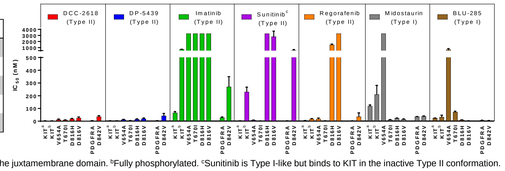


Figure 1. (A) Chemical structures of DCC-2618, active metabolite DP-5439, and analog DP-2976 (X-ray co-crystal structure). The compounds bind KIT and PDGFRA, including activation loop mutants, in a Type II or inactive conformation. **(B)** The phenyl ring of DP-2976 binds in the kinase "spine," as a surrogate for the exon 11 juxtamembrane domain inhibitory switch (disengaged due to phosphorylation or mutation). This surrogate for the inhibitory switch stabilizes the inactive state of KIT. **(C)** Surface representation of hydrophobic interactions in switch pocket regions by DP-2976. **(D)** Hydrogen bond network between DP-2976 and KIT. The upper box highlights direct H-bond interactions of DP-2976 with key switch residues. The lower box highlights an extended H-bond network nucleated by drug binding. Decoy switch Y823 (green) binds into this nucleated pocket, stabilizing an inactive KIT conformation. **(E)** Electronic and hydrophobic interactions with switch residues C809 and F811 stabilize the activation loop (green) in an inactive conformation.

DCC-2618 Broadly Inhibits KIT and PDGFRA Mutants

Figure 2

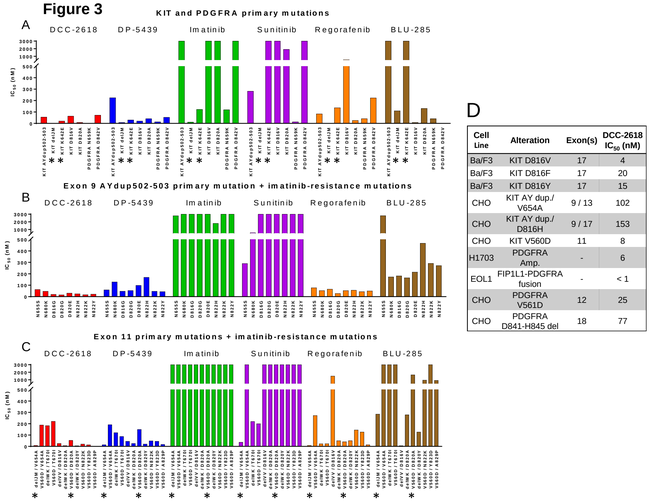
Mutation	Exon
KIT V654A	13
KIT T670I	14
KIT D816H	17
KIT D816V	17
PDGFRA D842V	18



[a]Phosphorylated on the juxtamembrane domain. [b]Fully phosphorylated. [c]Sunitinib is Type I-like but binds to KIT in the inactive Type II conformation.

Figure 2. At relevant cellular levels of ATP (1 mM), DCC-2618 broadly inhibits KIT mutants in exons 11, 13, 14, and 17, and a PDGFRA exon 18 mutant. Other Type II inhibitors do not block exon 17 mutants such as D816V KIT, whereas Type I inhibitors have weaker activity for exon 13/14 mutants.

Figure 3



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Cell Line	Alteration	Exon(s)	DCC-2618 IC_{50} (nM)
Ba/F3	KIT D816V	17	4
Ba/F3	KIT D816F	17	20
Ba/F3	KIT D816Y	17	15
CHO	KIT AY dup./ V654A	9 / 13	102
CHO	KIT AY dup./ D816H	9 / 17	153
CHO	KIT V560D	11	8
H1703	PDGFRA Amp.	-	6
EOL1	FIP1L1-PDGFRA fusion	-	< 1
CHO	PDGFRA V561D	12	25
CHO	PDGFRA D841-H845 del	18	77

Figure 3. DCC-2618 broadly inhibited KIT or PDGFRA phosphorylation in a panel of GIST cells (*) or transfected CHO cells expressing **(A)** GIST primary mutations; or imatinib-resistant KIT mutations with **(B)** exon 9 or **(C)** exon 11 primary mutations. The primary mutation (e.g. exon 9 or exon 11 V560D) in the context of the secondary mutation can have a significant impact on inhibition by some compounds. **(D)** DCC-2618 was also tested in other cells with KIT or PDGFRA alterations.

Figure 4

Cell Line	Type	KIT Mutation(s)
GIST T1	GIST	exon 11 del.
GIST 5R	GIST	exon 11 del. exon 14 T670I
GIST Juke	GIST	exon 11 del. exon 17 D816E
P815 (murine)	mast cell	exon 17 D814Y
Kasumi-1	AML	exon 17 N822K
HMC1.1	mast cell	exon 11 V560G
HMC1.2	mast cell	exon 11 V560G exon 17 D816V

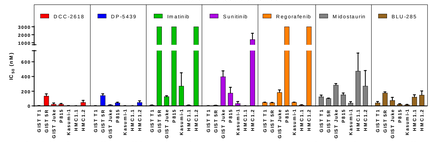


Figure 4. DCC-2618 also potently blocks cell proliferation in GIST, mastocytosis, and AML cells with imatinib-sensitive and imatinib-resistant KIT mutations, including exon 17.

DCC-2618 Inhibits KIT and PDGFRA-driven Xenografts

Figure 5

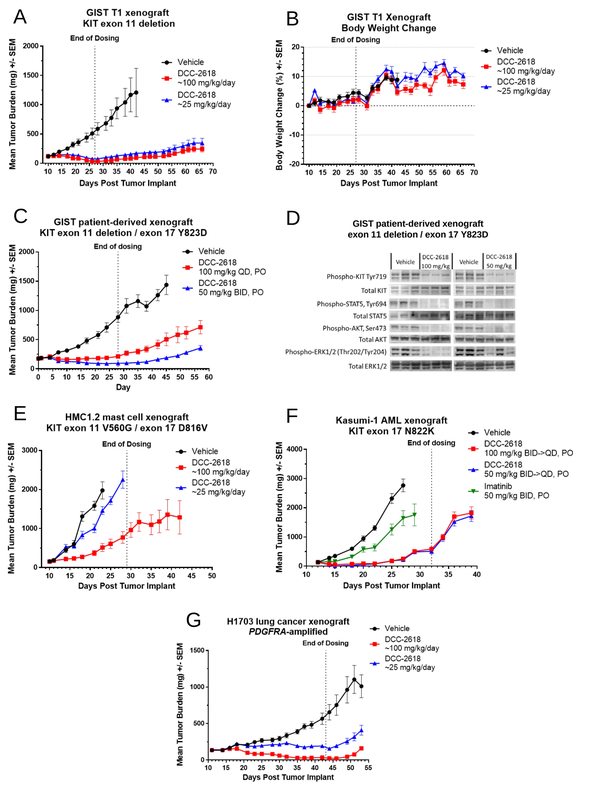


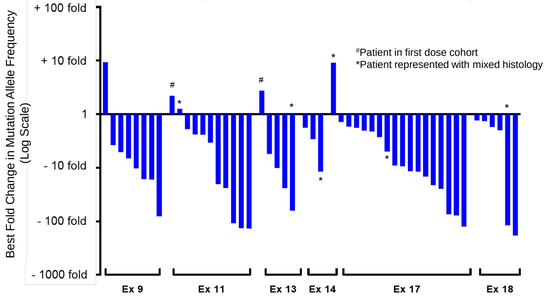
Figure 5. DCC-2618 blocked tumor growth in xenograft models driven by KIT mutants or PDGFRA-amplification. **(A)** GIST T1 (KIT exon 11 del.) tumor growth in mice treated with DCC-2618 formulated into the diet at 100 mg/kg/day (red) or 25 mg/kg/day (blue). Data are represented as mean ± SEM. **(B)** Treatments in this model were well tolerated as determined by body weight change. **(C)** GIST patient-derived xenograft (PDX; KIT exon 11 del. / exon 17 Y823D mutation) in mice treated with DCC-2618 dosed orally at 100 mg/kg QD (red) or 50 mg/kg BID (blue). **(D)** Inhibition of KIT autophosphorylation and downstream phosphorylation of STAT5, AKT, and ERK1/2 in GIST PDX tumors. **(E)** HMC1.2 mast cell xenograft (KIT exon 11 V560G / exon 17 D816V) in mice treated with DCC-2618 at 100 mg/kg/day (red) or 25 mg/kg/day (blue). **(F)** Kasumi-1 AML xenograft (KIT exon 17 N822K) in mice treated with DCC-2618 dosed orally at 100 mg/kg (red) or 50 mg/kg (blue), or imatinib at 50 mg/kg. **(G)** H1703 lung cancer xenograft (PDGFRA-amplified) in mice treated with DCC-2618 at 100 mg/kg/day (red) or 25 mg/kg/day (blue).

Saturation Mutagenesis

- Of relevance to GIST, no secondary KIT mutations were identified in a saturation mutagenesis study using Ba/F3 cells expressing KIT exon 11 mutant V560D at DCC-2618 concentrations of 25 nM – 100 nM
- Of relevance to mastocytosis, no secondary KIT mutations were identified in a saturation mutagenesis study starting with Ba/F3 cells expressing KIT exon 17 mutant D816V at a DCC-2618 concentration of 500 nM

Broad Decrease of Heterogeneous KIT Mutants in ctDNA from GIST Patients

Figure 6 Mutant allele fraction reductions from baseline for Exons 9, 11, 13, 14, 17, and 18. Patients with detectable plasma cfDNA at baseline and at least one follow up are included



[a]Figure reproduced from: Somaiah N., Razak A., Gordon M., Janku F., Flynn D., Kaufman M., Pitman J., Ruiz-Soto R., Smith B., Westwood D. Jennings J., Greensmith D., Jacobson J., Rosen O., and George S. (2017) DCC-2618, a novel pan-KIT and PDGFRA kinase switch control inhibitor demonstrates encouraging activity in patients with Gastrointestinal Stromal Tumors. CTOS Annual Meeting, Maui, HI.

Figure 6. Prior presentation of Phase 1 clinical trial data revealed multiple responses in heavily-pretreated GIST patients. Analysis of circulating tumor DNA (ctDNA) from this trial has shown decreases in mutant KIT ctDNA in GIST patients (n=19) across the spectrum of exons 9, 11, 13, 14, 17, and 18, including exon 9 AY duplications, exon 11 mutations and deletions, and difficult to treat mutations such as exon 13 K642E & V654A, exon 14 N680K, exon 17 activation loop mutations C809G, D816E, D820G/N/Y, N822K, & Y823C/D, V824M and exon 18 A829P and S840N.[a]

Summary

- DCC-2618 is a Type II switch control kinase inhibitor of KIT and PDGFRA, forcing even aggressively activated kinase mutants into Type II inactive conformations (Figure 1)
- DCC-2618 broadly inhibits primary and drug-resistant KIT mutants and primary PDGFRA mutants in enzyme assays at relevant levels of ATP (1 mM; Figure 2) and broadly inhibits primary and drug-resistant KIT mutants and primary PDGFRA mutants in a panel of GIST, mastocytosis, leukemia, lung cancer, and transfected cell assays (Figures 3 and 4)
- In xenograft studies, DCC-2618 blocked KIT and PDGFRA-driven tumor growth, including of KIT exon 17 mutants found in GIST (Y823D), AML (N822K), and mastocytosis (D816V) models (Figure 5)
- Compared to the approved and investigational compounds tested, DCC-2618 and its active metabolite, DP-5439, exhibit the broadest profile of inhibition across primary and secondary drug-resistant KIT mutations, and primary mutations in PDGFRA
- Translational data from the Phase 1 clinical trial has shown that DCC-2618 decreases mutant KIT ctDNA across the spectrum of KIT exons 9, 11, 13, 14, 17, and 18 in heavily-pretreated GIST patients (Figure 6)
- DCC-2618 is currently in a Phase 1 clinical trial in KIT and PDGFRA-driven cancers (ClinicalTrials.gov Identifier: NCT02571036) and in a Phase 3 clinical trial in GIST patients who have progressed on or are intolerant to imatinib, sunitinib, and regorafenib (ClinicalTrials.gov Identifier: NCT03353753)