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Use of a KIT-specific monoclonal antibody to bypass imatinib resistance in gastrointestinal stromal tumors

Badreddin Edris[1,2], Stephen Willingham[3], Kipp Weiskopf[3], Anne K Volkmer[3], Jens-Peter Volkmer[3], Thomas Mühlenberg[4], Irving L Weissman[1,3], and Matt van de Rijn[1,*]

[1]Department of Pathology; Stanford University School of Medicine; Stanford, CA USA; [2]Department of Genetics; Stanford University School of Medicine; Stanford, CA USA; [3]Institute for Stem Cell Biology and Regenerative Medicine and the Ludwig Cancer Institute; Stanford University School of Medicine; Stanford, CA USA; [4]Sarcoma Center; West German Cancer Center, University of Duisburg-Essen Medical School; Essen, Germany

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Abbreviations: GIST, gastrointestinal stromal tumor; ICC, interstitial cells of Cajal; mAb, monoclonal antibody

Acquired resistance to imatinib is a significant problem for the clinical management of gastrointestinal stromal tumor (GIST) patients, and second-line small molecules have shown limited efficacy in this setting. We have recently demonstrated that a monoclonal antibody targeting KIT could potentially bypass imatinib resistance in preclinical models of GIST.

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract and arise from the interstitial cells of Cajal (ICCs), which normally control the peristaltic contractions of the muscle wall. ICCs are characterized by the expression of the receptor tyrosine kinase KIT (CD117), a positive regulator of both mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) signaling pathways. Of the 95% of GISTs that express KIT, 70–80% exhibit activating mutations in *KIT*, often resulting in the transduction of a constitutive proliferative signal that drives tumor growth and progression.[1]

Imatinib, an ATP-competitive small molecule tyrosine kinase inhibitor initially developed to interrupt BCR-ABL signaling in subjects affected by chronic myelogenous leukemia, is one of the hallmark examples of modern targeted anticancer therapy. Imatinib was soon discovered to inhibit KIT signaling by stabilizing the receptor in an inactive conformation, thereby limiting cell proliferation. Consequently, it was evaluated as a therapeutic option for GIST patients, causing clinical outcomes to improve dramatically.[2–5] Prior to imatinib, only 5% of GIST patients responded to conventional chemotherapy, and the median survival was 18 months. Following the introduction of imatinib, response rates soared to 70–85%, and the median survival reached 5 y. Unfortunately, in most cases secondary *KIT* mutations arise and eventually enable GISTs to proliferate in the presence of imatinib. Thus, additional therapeutic options are required for the clinical management of imatinib-resistant GIST patients. Most approaches to date have focused on the development of second-generation KIT inhibitors, the identification of small molecules targeting downstream transducers of KIT-conveyed signals, or the blockage of KIT-unrelated proteins implicated in GIST growth. In an alternative approach, we have recently sought to investigate whether SR1,[6] a monoclonal antibody (mAb) specific for KIT, would slow the growth of imatinib-resistant GISTs.[7]

First, we demonstrated that SR1 is able to slow the growth of three primary human GIST cell lines (two of which deriving from patients that had developed imatinib resistance) in vitro. Importantly, the reduction of cell viability observed in the presence of SR1 was equivalent in imatinib-sensitive and -resistant cell lines. Besides blocking signal transduction, mAbs targeting cell surface proteins can also enable robust antitumor innate immune responses. Therefore, we next evaluated whether SR1 would operate as an opsonin and allow macrophages to engulf GIST cells in vitro. We found that the binding of SR1 to KIT-expressing tumor cells increased their phagocytic uptake by macrophages, irrespective of their original sensitivity to imatinib (**Fig. 1**).

To build upon our in vitro findings, we next tested the efficacy of SR1 in two xenograft models of GIST. To this aim, we established imatinib-sensitive GISTs in mice, a setting in which SR1 significantly repressed tumor growth by approximately 5-fold. Along similar lines, SR1 was effective against an imatinib-resistant GIST xenograft, inhibiting tumor growth by 10-fold. Taken together, these results

*Correspondence to: Matt van de Rijn; Email: mrijn@stanford.edu
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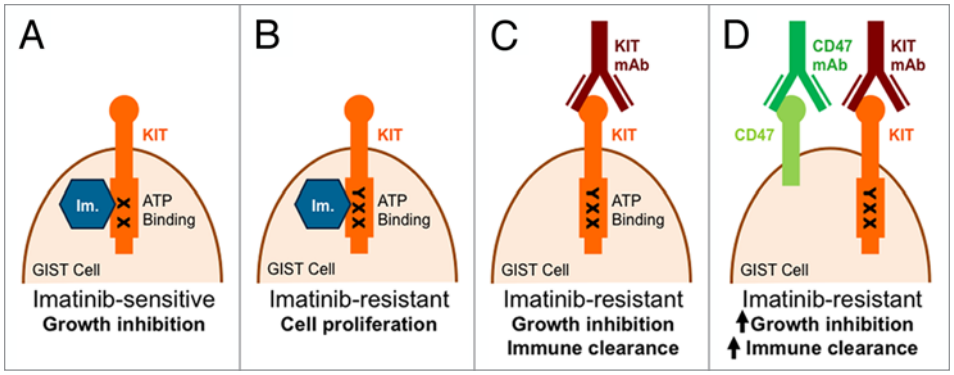

Figure 1. Use of a monoclonal antibody to bypass imatinib resistance in gastrointestinal stromal tumors. (**A**) Mutations (X) in *KIT* constitutively activate the KIT pathway but leave gastrointestinal stromal tumor (GIST) cells sensitive to the antineoplastic effects of imatinib. (**B**) Nevertheless, GIST cells eventually develop secondary *KIT* mutations (Y) that enable them to proliferate in the presence of imatinib. (**C**) We have recently shown that SR1, an anti-KIT monoclonal antibody (mAb), can inhibit the growth of GIST cells that have become resistant to imatinib and enable their clearance by immune effector mechanisms. (**D**) In the future, a combinatorial regimen involving a second mAb, for instance targeting CD47, may turn out to further enhance the therapeutic effects of SR1.

demonstrate the therapeutic potential of KIT-targeting mAbs against GISTs, regardless of whether tumors have become resistant to imatinib.

In the future, it may be possible to further increase the efficacy of SR1 by combining it with additional mAbs. We have recently demonstrated that anti-CD47 mAbs, which disrupt the inhibitory interactions between CD47 on the surface of cancer cells and the macrophagic receptor signal-regulatory protein α (SIRPα), enables the robust phagocytosis by macrophages of sarcoma and carcinoma cells while dramatically decreasing tumor growth and metastatic spread.[8–10] One possible avenue of investigation would therefore evaluate the potential synergy of anti-KIT and anti-CD47 mAbs in blocking the growth of imatinib-resistant GISTs.

Our findings demonstrate that the clinically relevant problem of imatinib resistance in GIST may be bypassed by employing a KIT-targeting mAb, and provide the rationale to investigate the use of mAbs in addition to, or instead of, small molecules for the clinical management of GIST. Additionally, our findings identify KIT as a candidate target for the immunotherapy of GIST patients. In the near term, we aim to validate and build upon these promising results, with the ultimate goal of ameliorating the standard of care for GIST patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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