Re-engineering Dasatinib into an Immuno-synergic Drug

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Abstract

Immune checkpoint blockers revolutionized cancer therapy. Yet, they met only modest success when treating tumors where regulatory T cells recruited at the tumor periphery overwhelmingly suppress the adaptive immune response. To achieve lasting cure, we propose immuno-tuning combinations with purposely engineered targeted agents that block indirect tumor-induced immunosuppression without adversely impacting the adaptive response. In particular, we propose a redesign of dasatinib with three objectives: (1) to remove its nanomolar affinity towards LCK, a major signal transducer in the activation of T cells, thereby avoiding interference with the adaptive immune response, (2) to enhance its affinity towards c-KIT, a crucial receptor in the recruitment of regulatory T cells, thereby preventing tumor recruitment of immuno-modulatory elements, and (3) to enhance its affinity towards c-SRC, a major cancer target, thereby promoting a higher antigenic activity. We propose to combine this dasatinib variant with an immune checkpoint inhibitor to enhance the tumor susceptibility to immunotherapy.

Key Words: tumor-induced immunosuppression, checkpoint blocker, lymphocyte-specific kinase, stem-cell growth factor, adaptive immune response, regulatory T cell, immuno-tuning technology

Statement of purpose: This technical report is a contribution to the Open Drug Design Project whose goal is to foster transparent, rational design and testing of therapeutic agents to improve global health.

1 Overview

Combining checkpoint immunotherapies with targeted pharmaceuticals based on kinase inhibitors (KIs) has been the subject of recent intense scrutiny [1]. These combinations hold potential to
enhance the immune response because of the high antigenic activity promoted by KIs. However, certain KIs can also interfere with immunotherapy, reducing its effectiveness. One of the most powerful KIs, dasatinib, was flagged precisely for that reason [1], and correspondingly, dasatinib has not been pursued in combination with checkpoint immunotherapies for the treatment of cancer, in spite of its tremendous antigenic activity. To position this drug as a companion to immunotherapy, we present here one possible redesign of its chemical structure using wrapping technology to potentially enhance the effectiveness of dasatinib as a sensitizer to immune checkpoint blockade.

Dasatinib [2] (known commercially via the registered trademark Sprycel) is a kinase inhibitor with nanomolar or subnanomolar activity against major oncological targets like the constitutively active chimera bcr-ABL, c-KIT and PDGFR and the entire Src-family kinases, including c-SRC and LCK [2]. Ongoing clinical trials evaluate dasatinib for the treatment of solid tumors, including GIST (ClinicalTrials.gov Identifier NCT02776878) and ovarian cancer (ClinicalTrials.gov Identifier NCT02059265). However, a combination of dasatinib with immunotherapy to achieve a definite cure has not been attempted and may be forbiddingly challenging because dasatinib is one of the most powerful LCK inhibitors known ($K_D=0.2\text{nM}$).

The major dasatinib target LCK plays a key role as transducer of the T cell activation signals. Therefore its inhibition interferes adversely with the adaptive immune response that immunotherapy is intended to elicit. Therefore, the level of direct immunosuppression is extreme [3], making it dangerous even as monotherapy. Yet, dasatinib is a more powerful c-KIT inhibitor than imatinib, hence its potential to block tumor resistance to immunotherapy is probably greater. These properties suggest a challenge to re-engineer dasatinib to make it immune-synergic.

Another attractive feature of dasatinib is its high antigenic activity due to a powerful inhibition of c-SRC, a major cancer target that is homologous to LCK. We wish to retain the affinity to c-SRC while reducing affinity to LCK.

2 Wrapping technology applied to dasatinib redesign

Dehydrons are now widely recognized to be determinants of protein associations [4, 5]. Their impact as selectivity filters in drug design has been established [6, 7, 8, 9, 10], and results from the fact that dehydrons are not preserved across homologous proteins [11]. Recently, we have realized that dehydrons also stimulate enzymatic function, by inducing chemical basicity in the nearby aqueous interface [12]. These complementary insights suggest two ways to enhance the therapeutic efficacy of Dasatinib through rational, dehydron-based redesign with the following objectives:

1. to remove its nanomolar affinity towards LCK, a major signal transducer in the activation of T cells, thereby avoiding interference with adaptive immune response,

2. to enhance its affinity towards c-KIT, a crucial receptor in the recruitment of regulatory T cells, thereby preventing tumor recruitment of immuno-modulatory elements, and

3. to enhance its affinity towards c-SRC, a major cancer target, thereby promoting higher antigenic activity.

\[^1\]Harvard Medical School — Library of Integrated Network-based Cellular Signatures (HMS-LINCS) Kinome Scan Data/Last Update: September 15, 2016. url: http://lincs.hms.harvard.edu/kinomescan/
Figure 1: Region in dasatinib/c-SRC complex containing inducible M341-G344 backbone hydrogen bond that structurally aligns with dehydron C673-G676 in c-KIT. To induce the M341-G344 bond, the exogenous wrapping must be augmented through methylation of dasatinib at the position indicated by yellow dots, yielding the wrapperone compound. The resulting compound excludes the water molecule (oxygen as red ball, arrow) that disrupts M341-G344 bond formation. The chemical structure of the wrapperone is shown in the lower panel.

The achievement of these objectives hinges on the fact that dehydrons are non-evolutionarily-conserved promoters of protein association [11]. The plan here is to redesign Dasatinib in order to target selectively a dehydron present in C-Kit, but absent in LCK and inducible in c-SRC. We believe that it will be possible to achieve a design that fulfills the objectives without significantly altering the basic chemical structure of Dasatinib.

To address the challenge, we aligned all dasatinib targets and examined epistructural differences. Like with WBZ.4 target JNK [13, 14], the major dasatinib target c-SRC presents an inducible backbone hydrogen bond at position M341-G344 (Figure 1) that aligns with dehydron C673-C676 in c-KIT and with solvent-secluded M319-G322 bond in LCK (Figure 2). Methylation at the position indicated by yellow dots in Figure 1 induces the M341-G344 c-SRC hydrogen bond, enhancing the anti-c-SRC inhibitory power of dasatinib by further stabilizing the drug/target complex [15, 16]. This chaperone role through wrapping of a preformed hydrogen bond inspired the term “wrapperone”. The drug alteration also selectively removes LCK affinity following the same rationale that holds for WBZ.4 (cf. Figure 2). Furthermore, the wrapperone augments the wrapping of dehydron C673-G676 upon binding to c-KIT, hence stabilizing the drug/target complex. Thus, the wrapperone is expected to curb tumor-induced immunosuppression more strongly than dasatinib. The fact that this crucial effect is not overwritten by
direct LCK-related immunosuppression makes the wrapperone an ideal agent to synergize with immune-stimulating checkpoint blockades. Reciprocally, the checkpoint immunotherapies, that have proven only moderately successful to treat ovarian cancer [17], will be rescued through the wrapperone combination, since the potent and now unfettered anti-c-KIT activity significantly reduces the peripheral Tregs:Teff ratio and since the antigenic activity generated by drug-induced apoptosis of the cancer cell is significantly enhanced via c-SRC inhibition when adopting the wrapping variant.

3 Background

We have recently completed a redesign of Imatinib using our wrapping technology [5]. The redesign was done in collaboration with M. D. Anderson Cancer Center, and it was intended to reduce the Imatinib toxicities while retaining its therapeutic efficacy [9]. The resulting compound fulfilled our expectations, and it is now patented [18]. This provides a proof of concept of our dehydron-based engineering strategies.
4 Conclusions

We have proposed a modification of dasatinib by methylation at the position indicated by yellow dots in Figure 1. This modification must be tested experimentally to see if our stated objectives have indeed been achieved. If indeed the wrapping variant of dasatinib fulfills objectives (1.–3.), it will provide a powerful immuno-synergic agent to combat cancer.

References


