Methods Supplement

Cell culture and drug treatment

Human umbilical vein endothelial cells (HUVECs) and human monocytic U937 cells (ATCC, CRL-1593.2) were cultured as described[1,2]. HUVECs were treated with vehicle (DMSO) or each TKI at a concentration consistent with the steady-state peak plasma concentration (Cmax) reported in CML patients: Dasatinib (0.2 μM)[3], Ponatinib (0.1 μM)[4], Nilotinib (3.0 μM)[5], Imatinib (4.0 μM)[6], Bosutinib (0.5 μM)[7].

Cell survival assay

HUVECs were seeded in a 96-well plate at 1500 cells/well. After 20 hours of TKI treatment, cell survival was quantified using the CellTiter-Glo Luminescent Assay (Promega).

Leukocyte adhesion assay

HUVECs cultured to 90% confluence were treated with TKIs for 20 hours and incubated for 2 hours with fluorescently labeled (Molecular Probes; Eugene, OR) U937 leukocytes as described[1]. Adherent cells were counted by a blinded investigator**.**

Wound healing assay

A scratch "wound" was generated in sub confluent HUVECs with a sterile pipette tip and ECs were allowed to migrate into the wound in the presence of TKIs for 20 hours as described[8]. ECs in the wound were counted by a blinded investigator.

P100 phosphoproteomic assay

HUVECs grown to confluence in 100 mm plates were treated with TKIs in triplicate for 3 hours. The reduced representation P100 phosphoproteomic mass spectrometry assay was performed and data processed as previously described[9]. The P100 assay is a "sentinel" assay that monitors a group of phosphosites known to report broadly on signaling activity in response to drugs[10].

Statistical data analysis of P100 data

Morpheus (https://software.broadinstitute.org/morpheus) was used to perform marker selection[11] to identify phosphosites that differentiated the toxic (dasatinib, ponatinib, nilotinib) from the non-toxic (imatinib) TKIs with $p<0.05$ and false discovery rate $q<0.25$ (metric: signal-to-noise; permutations: 1000). A similarity matrix was computed using the 11 selected phosphosites (Pearson correlation). The diagonal (identity) was discarded and replicate comparisons were averaged to compute aggregate similarity within or across drugs.

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