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Comment on mr-2022-6

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Community comment on "Imatinib disassembles the regulatory core of Abelson kinase by binding to its ATP site and not by binding to its myristoyl pocket" by Stephan Grzesiek et al., Magn. Reson. Discuss., https://doi.org/10.5194/mr-2022-6-CC1, 2022

The manuscript by Grzesiek and colleagues questions the validity of the main finding of Xie et al. (JMB 2022) that claims binding of imatinib to Abl's myristoyl binding pocket and thereby promoting disassembly of the regulatory SH3-SH2-kinase domain core of Bcr-Abl. Strong data is provided by Grzesiek et al. that convince me that the model of Xie et al. cannot be correct. It is also important that Grzesiek et al. listed points on insufficient reporting of experimental details that prevent reproduction of the data by others.

In addition, I would like to make some more general points that question the biological/medical relevance of the findings of the Xie et al. paper:

Xie et al. report a Kd for imatinib binding to the myristoyl binding pocket that is 2-3-fold above the reported average trough plasma concentration for imatinib in CML patients that received the standard dose (400 mg once daily) of the drug. Hence, only a low occupancy of the myristoyl pocket at clinically achievable imatinib concentration can be expected, in particular as the intracellular concentration of imatinib will likely be lower than the plasma concentration. Therefore, this is an epiphenomenon that can be observed in vitro at very high imatinib concentration, but without physiological relevance for BCR-ABL biology and CML treatment.

Secondly, whether imatinib is able to bind the myristoyl pocket in full-length Bcr-Abl remains to be determined. It is important to point out that the initial data in Xie et al. was obtained with a construct encoding only the kinase domain, i.e. lacking the regulatory SH3 and SH2 domains, as well as lacking several hundred amino acids at the C-terminus. In addition, a further truncation of the C-terminal alpha I-helix was necessary to obtain the crystal structure with imatinib bound to the myristoyl binding pocket. Therefore, biochemical and cellular assays with full-length Abl/Bcr-Abl are necessary to rule out the possibility that imatinib binding to the myristoyl pocket is an artefact of this highly engineered Abl construct. At this point, it is also important to clarify that the possible binding of imatinib to the myristoyl pocket of ABL kinases is not novel and was already described a decade ago: Salah et al. (J Med Chem (2011) *54*(7), 2359-67) showed by ITC and a co-crystal structure of the ABL2 kinase domain (which is almost identical to ABL1) that imatinib may be able to bind the myristoyl pocket. Importantly, Salah et al. also used a C-terminally truncated alpha I-helix construct of the kinase domain, but recognized possible issues and hence interpreted their data much more cautiously. They concluded: "It is clear from the ABL2: imatinib structure that in the full-length protein imatinib would

not bind in the myristate binding pocket in such a way that would cause inhibition by promoting the bending of helix alpha-I’ and the docking of the SH2 and SH3 domains due to a steric clash with a bent helix alpha-I’.”