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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-CC2, 2022

The manuscript by the Grzesiek lab critically addresses a recent publication by the Kalodimos group claiming that imatinib binding to the myristoyl pocket, and not binding to the active site, opens full-length Abl kinase.

This is a well-written manuscript with new experimental data that very clearly demonstrates and discusses the overwhelming evidence that the previously published mechanism (nanomolar imatinib binding to the active site) opens full-length Abl kinase is correct. Grzesiek et al. deliver an important contribution to the scientific community to logically discuss the experimental flaws in the paper of question by Xie et al (JMB 2022) that led to an incorrect model, so that the non-experts can follow this scientific dispute. I completely agree with the all points made in this new manuscript that was submitted to Magnetic Resonance Grzesiek et al., which reflects our original response to the manuscript by Xie et al (JMB 2022), and agrees with experimental data of our lab. Since the Grzesiek lab provided a clear argumentation for their model, and point out the scientific issues in the Kalodimos publication that led to incorrect conclusion I will not elaborate in detail here again. I will just highlight the most important issues:

Central to Kalodimos' proposal that imatinib binding to the myristoyl pocket is causing the opening of full-length kinase (and NOT binding to the active site with nanomolar affinity!) are ITC experiments performed on the catalytic domain only. This is quite irrelevant for the question, why did the authors not perform ITC for the full-length kinase? Along the same argument, their x-ray structure that shows imatinib bound to the allosteric site could only been obtained for the kinase domain that even has the crucial alpha I helix truncated!

A major hindrance when reading the Kalodimos paper has been the lack of information, it cannot be followed which kinase constructs were used in the different experiments (as example Fig. 2 legend: "Crystal structure of Abl in complex with imatinib bound to its allosteric pocket", this is not Abl, it is Abl kinase domain with a truncated alpha helix), or which concentrations were used in different experiments. Trying to estimate the concentrations for the ITC experiments (the single experiment that was used to determine the affinity of imatinib to the allosteric site to be 10 uM, the new finding of the manuscript): The data seem to suggest an N-value of about ~7, which means with 70uM Abl kinase domain, the Gleevec concentration used in the syringe would be ~1000uM, where it is known that imatinib precipitates above 70 uM. Therefore, the heat profiles in Supplementary Figure 5 may be a mixture of dissolving precipitated Gleevec into the cell

and Gleevec binding to the allosteric site (if measurable).

In summary, it would be of great interest to the broader scientific community to publish this submitted manuscript asap. Scientific advance is rooted on clean experimental data, logic data interpretation, and importantly open scientific discussions and arguments. Publications like this one by the Grzesiek lab allows the reader to independently evaluate both opposing models of imatinib action and to draw their own conclusions, the central power of scientific publishing.