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Magn. Reson. Discuss., referee comment RC2
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Comment on mr-2022-6

Anonymous Referee #1

Referee 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-RC2, 2022

A recent PNAS article has come to the attention of this reviewer that may deserve consideration by the authors. The article reports the results of nanoBRET experiments in HEK293T cells to measure the dissociation of imatinib from wild-type Abl fused with NanoLuc luciferase *in vivo*. The half-life time of the complex was determined to be about 20 min. (Lyczek et al., 2021), in agreement with the slow exchange regime indicated by the NMR experiments of the present article. Interestingly, some of the imatinib resistance mutants showed practically unchanged IC_{50} values, but their dissociation rates were increased, suggesting that the more rapid decrease of inhibition can lead to lesser efficacy in patients despite nominally unchanged dosage.

Lyczek, A., Berger, B.-T., Rangwala, A. M., Paung, Y., Tom, J., Philipose, H., Guo, J., Albanese, S. K., Robers, M. B., Knapp, S., Chodera, J. D., and Seeliger, M., Mutation in Abl kinase with altered drug-binding kinetics indicates a novel mechanism of imatinib resistance, Proc. Natl. Acad. Sci., 118, e2111451118, https://doi.org/10.1073/pnas.2111451118j1of10, 2021.