Reply to Valadares and Woo: Mechanism of Rv2837c from *Mycobacterium tuberculosis* remains controversial

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This is a response to a letter by Valadares and Woo (1).

In an Addition and Correction, we tried to show that Mol A and B were captured in different reaction states. The two AMP molecules that were revealed by electron density in Mol B are in good shape and quite distinct from the molecule in Mol A described in our published paper (2). The flash-frozen crystal is a mixture of free Rv2837c, c-di-AMP–bound Rv2837c, pApA-bound Rv2837c, double-AMP–bound Rv2837c, single-AMP–bound Rv2837, even in transition states as well. It is understandable that those familiar with a perfect single crystal would have concern. The 5′-pApA was built as a nanoRNA of "AA." We appreciate what Drs. Valadares and Woo pointed out in their letter. Similar flaws do happen but rarely detour the understanding of the catalysis.

As for the activity of Rv2837c on c-di-GMP, the data we have reported solidly support what has been observed from the structures. It is clear that Gentner's paper (3) supports rather than opposes our argument. Gentner *et al.* mentioned that c-di-GMP oligomerizes at high concentrations and becomes a monomer at physiological concentrations. Recently, Dey *et al.* (4) repeated the central part of the biochemistry in our paper and confirmed our result.

At last, we agree with Valadares and Woo that more work is needed to clearly elucidate the hydrolytic process of 5′-pApA. Such elucidation of the kinetic process is far beyond the discussion of our paper since understanding the break and formation of chemical bonds needs the support of theoretical calculation involving quantum chemistry.

The authors declare that they have no conflicts of interest with the contents of this article.

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