Mechanism of Rv2837c from *Mycobacterium tuberculosis* remains controversial

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Napoleão Fonseca Valadares[‡1] **and James Woo**[§]

From the [‡]*Laboratory of Molecular Biophysics, Department of Cell Biology, University of Brasília, Brasília -DF, 70910–900, Brazil and the* [§]*Department of Biochemistry and Molecular Biology, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois 60064*

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In the Additions and Corrections to their original paper, He *et al.* (1) claim to present a better model to replace their previous Rv2837c crystal structure; nevertheless, their novel model raises a series of concerns. The 5′-pApA molecule is missing an oxygen atom in the phosphate group of the carbon 5 of the ribose ring in the deposited model and in Figs. 10 and 11. Moreover, several methodologies, including the PDB_REDO (2) and the Uppsala Electron Density Server (3), fail to reproduce the electron density maps presented in Figs. 10 and 11. In fact, the modeled position of the proposed catalytic water molecule is not supported by electron density, and refining the data using AMP instead of 5′-pApA yields improved refinement statistics and a better ligand real-space correlation coefficient. Additionally, the atomic distances presented in Fig. 7 (1) are not consistent with the deposited structures. These observations indicate that the catalytic mechanism proposed by the authors is not supported by their electron density data.

Cyclic dinucleotide signaling controls central aspects of bacterial physiology, and well-designed assays demonstrated that Rv2837c is a c-di-AMP–specific enzyme (4). Nevertheless, He *et al.* (1) insist that Rv2837c is also specific to c-di-GMP even when their own enzyme kinetic data indicate otherwise. To justify the considerably higher activity of Rv2837c toward c-di-AMP observed in their assays, the authors propose that the slow hydrolysis of c-di-GMP is a consequence of its oligomeric state. However, it has been shown that c-di-GMP dimers are in fast exchange with the monomers and that c-di-GMP is monomeric at the concentrations employed even in the presence of Mg^{2+} (5). In conclusion, the mechanism of Rv2837c remains to be elucidated.

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

[1] To whom correspondence should be addressed. E-mail: napo@unb.br.

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