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# *Cis*-2 and *trans*-2-eicosenoic fatty acids are novel inhibitors for *Mycobacterium tuberculosis* protein tyrosine phosphatase A

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**Small protein tyrosine phosphatase (PtpA) of *Mycobacterium tuberculosis* (Mtb) is attributed to the development of latent tuberculosis infections, and hence becomes an interesting target for drug development. In this communication, inhibition of PtpA by naturally occurring fatty acids: *cis*-2 and *trans*-2-eicosenoic acids is investigated. Mtb PtpA was heterologously expressed in *Escherichia coli*, and the activity of PtpA was inhibited by *cis*-2 and *trans*-2 eicosenoic fatty acids. Both compounds showed strong inhibition of PtpA activity, with $IC_{50}$ at low micromolar concentrations. In comparison, *trans*-11-eicosenoic acid only slightly inhibited PtpA. *In silico* analysis confirmed the inhibition of PtpA by *cis*-2-eicosenoic acid by formation of several hydrogen bonds. These findings show that *cis*-2 and *trans*-2 eicosenoic fatty acids are potential candidates for latent tuberculosis inhibitors.**

**Key words**: *Mycobacterium tuberculosis*, latent infection, protein tyrosine phosphatase A, *cis*-2 and *trans*-2 eicosenoic fatty acids

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**Abbreviations**: CAD, computer aided drug discovery; MDR TB, multi-drug resistant tuberculosis; LAM, lipoarabinomannan; LTBI, latent TB infection; XDR TB, extensively drug-resistant TB; PknG, protein kinase G; PtpA, protein tyrosine phosphatase A

## INTRODUCTION

*Mycobacterium tuberculosis* pathogen is one of the most devastating pathogens with high mortality all over the world. The death toll caused by this infection is worsened by increasing HIV infection cases. This figure is even more complicated by the development of antibiotic resistant strains: multi-drug resistant tuberculosis (MDR TB) and extensively drug-resistant TB (XDR TB). The battle against TB has an additional front, i.e. latent TB infection (LTBI). It is estimated that 1.7 billions of people, or approximately one quarter of the world's population, are infected with these bacteria in the latent infection fashion (World Health Organization, 2019; Houben & Dodd, 2016), and 10% of those individuals develop active infection at a later stage of their life (Vynnycky & Fine, 2000; Stutz *et al.*, 2018).

The ability of the bacteria to avoid the acidic lysosomal degradation within host macrophages has been recognized as one of the survival mechanisms of *M. tuberculosis* from phagolysosome degradation, and leads the bacterium to its latent phase (Pieters & Gatfield, 2002), where it further utilizes nutrition from its host for long term dormancy (Mali & Meena, 2018). Although several bacterial survival factors, such as the protein tyrosine phosphatases, bacterial lipoarabinomannan (LAM) and protein kinase G (PknG) have been extensively suggested to be involved in the latent infection (Li & Xie, 2011; Janssen *et al.*, 2012), the mechanism by which latent TB infection develops into its active state is not fully understood. Nevertheless, inhibition of latency factors opens up the research field to combat bacteria even before latency is established.

Among the proteins associated with the development of latent TB infection is protein tyrosine phosphatase A (PtpA). This protein is known to be responsible for inhibition of fusion even between phagosome and lysosome. In a normal endocytosis pathway, once the bacterium is engulfed by the macrophage cell, the resulted mycobacterial-laden phagosome recruits host vacuolar-$H^+$-ATPase (V-ATPase) that acidifies the endosome, a precondition required later when it fuses with the lysosome and thus ensuring that a suitable environment for hydrolytic enzymes of the lysosome is formed (Sun-Wada *et al.*, 2009; Stutz *et al.*, 2018; Upadhyay *et al.*, 2018). However, bacterium develops a survival strategy by secreting PtpA that permeates the phagosome membrane and binds to the subunit H of V-ATPase in the macrophage cytosol. PtpA is also reported to dephosphorylate vacuolar sorting protein VPS33B which is required for the fusion of endocytic organelles. The binding of subunit H of V-ATPase and dephosphorylation of VPS33B by mycobacterial PptA are concerted evens that account for the hindrance of bacteria to enter phagolysosome degradation (Bach *et al.*, 2008; Wong *et al.*, 2011; Korb *et al.*, 2016). PtpA was also reported to supress the host innate immunity by regulating host gene expression (Wang *et al.*, 2017). From this point of view, PtpA, along with other effector proteins, becomes an interesting target for anti-latent TB drug development.

Several attempts to discover novel drugs benefitted from the progress in the computer aided drug discovery (CAD). A recent example of this approach has been underlined by Zhang and co-workers who reported a thiobarbiturate compound as a novel Mtb PtpB inhibitor with an $IC_{50}$ of 22.4 μM (Zhang *et al.*, 2019). Furthermore, a thiosemicarbazone compound predicted by molecular modelling has been synthesized and revealed its inhibitory effect on Mtb PtpA with a low micromolar $IC_{50}$ (Sens *et al.*, 2018). A comprehesive review of *in silico*

studies targetting tubercular protein is presented by de Oliveira Vianaand others (de Oliveira Viana *et al.*, 2018). A recent *in silico* study by Dhanjal and co-workers has suggested that eicosenoic fatty acid derivative, the *trans*-2 eicosenoic acid. might inhibit Mtb PtpA and a related phosphatase of Mtb, PtpB (Dhanjal *et al.*, 2014). The present study aims at testing the ability of *trans*-2-eicosenoic fatty acid to inhibit Mtb PtpA.

## MATERIALS AND METHODS

**Materials**. Plasmid and *Escherichia coli* strains. Recombinant plasmid pET30b-PtpA was a kind gift from Prof. Yossef Av-Gay, Univesity of British Columbia, Canada. The plasmid was maintained in *Escherichia coli* XL1-Blue, and for expression, *E. coli* BL21(DE3) was used. Bacteria were grown in LB medium containing 0.5% yeast extract, 1% NaCl, 1% bacto trypton and 30 µg/mL kanamycin (USP Biobasic). Agar LB medium was made by addition of 2% bacto agar. All ingredients were from major biochemical vendors.

**Chemicals**. All reagents for buffers were from major chemical vendors. *Cis*-2-eicosenoic and *trans*-2-eicosenoic fatty acids were purchased from Larodan AB (Sweden). *Trans*-11-eicosenoic fatty acid and *para*-nitrophenyl phosphate were from Sigma-Aldrich.

**Methods**. Expression of Mtb protein tyrosine phosphatase A in *E. coli*. Recombinant plasmid pET30b-PtpA was introduced into competent *E. coli* BL21(DE3) cells by electroporation (Gene Pulser Electroporation Systems, Bio-Rad). For PtpA production, an overnight pre-culture of transformed cells was added to 250 mL LB medium in an Erlenmeyer flask containing kanamycin. Cells bearing PtpA gene at log phase ($OD_{600}$ of c.a. 0.6) were induced by addition of 0.5 mM isoprophyl beta-thiogalactose (IPTG, Sigma-Aldrich) and kept in a rotary shaker for 4 hours at 37°C, 250 rpm. Cells were harvested by centrifugation at 3500 rpm and cell pellet was resuspended in phosphate buffered saline (PBS: 137 mM NaCl, 2.7 mM KCl, 8 mM $Na_2HPO_4$ and 2 mM $KH_2PO_4$) prior to lysis by 10 cycles of sonication (30 seconds sonication and 30 seconds pause). Clear lysate containing PtpA was obtained by centrifugation at 12000 rpm, 4°C for 30 min.

Protein concentration was determined by bicinchoninic acid (BCA kit, Thermo scientific). Sodium dodecylsulfate polyacrylamide gel electrophoresis was performed to show the expression of PtpA in *E. coli*. Samples were subjected to electrophoresis in 12.5% polyacrylamide gel.

The activity PtpA was tested for its phosphatase activity against *para*-nitrophenyl phosphate (p-NPP) as modified from (Mascarello *et al.*, 2013). Reaction mixture contained 6 mM pNPP substrate and 100 µM imidazole was added to final volume of 180 µL, followed by pre-incubation at 37°C for 5 minutes prior to addition of 20 µL of PtpA (1 µg/µL). Reaction was allowed to proceed and the resulted *para*-nitrophenol was measured at 410 nm every 2 minutes for 30 minutes.

**Inhibition of PtpA by eicosenoic fatty acids**. -o test the inhibitory effect of eicosenoic fatty acids, PtpA was allowed to hydrolyze substrate *para*-nitrophenyl phosphate in the absense or presense on various concentrations of *trans*-2-eicosenoic acid, *cis*-2-eicosenoic acid, and *trans*-11-eicosenoic acid, ranging from 0 µM to 30 µM, for 30 minutes at 37°C. Lysate of untransformed *E. coli* BL21 was used as control in each experiments.

The inhibitory effect of eicosenoic fatty acid isomers on the activity of PtpA was depicted as the decrease in absorbance ($A_{410}$ nm) by the increment concentration of eicosenoic fatty acids. The $IC_{50}$ values for each eicosenoic fatty acid were calculated with the use of Prism 7 (GraphPad).

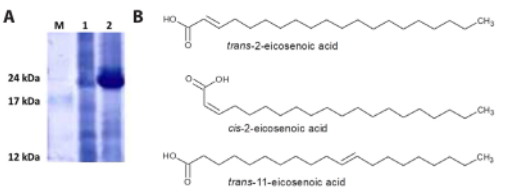


**Figure 1. A. In each lane, 20 µg of samples were loaded onto 4.5% focusing gel and 12.5% resolving polyacrylamide gel for separation.**
Overexpressed PtpA in ***Escherichia coli*** BL21(DE3) appears as a major band at 18 kDa which corresponds to PtpA (lane 2). Lane 1 is uninduced sample. B. Three isomers of eicosenoic fatty acid structures generated by Chemdraw, tested for their inhibitory effect on Mtb PtpA activity: ***trans***-2-eicosenoic acid, ***cis***-2-eicosenoic acid and ***trans***-11-eicosenoic acid.

**Docking**. Interaction of eicosenoic fatty acids with PtpA that lead to inhibitory of phosphatase activity was analyzed with the Discovery studio (Accelrys, San Diego, CA, USA). The PtpA protein that contains native ligand glycerol (PDB accession number 1U2Q) was used for docking with each of the eicosenoic fatty acids. Ligands, i.e. the eicosenoic fatty acids, were prepared by Chemdraw (Fig. 1B).

## RESULTS

### Expression of PtpA in *E. coli*

PtpA, cloned into the pET30b plasmid, was successfully expressed in *E. coli* BL21(DE3) under T7 promoter and induced by 0.5 mM isopropyl beta-thiogalactose (IPTG) as described by Studier and others (Studier *et al.*, 1990). PtpA appears as a protein of c.a. 18 kDa (Fig. 1A), which is in agreement with another report (Chiaradia *et al.*, 2008). Activity of overexpressed PtpA was assayed by measuring its ability to hydrolyze *para*-nitro-

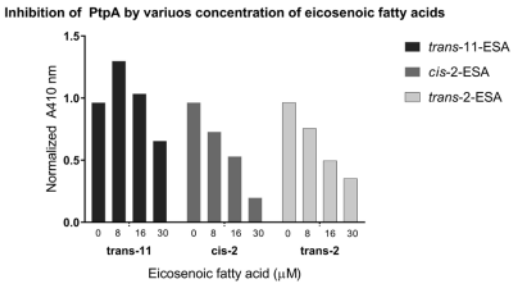


**Figure 2. Inhibition study of overexpressed PtpA with increasing concentration of eicosenoic fatty acids (ESA) at 0, 8, 16 and 30 µM.**
The *trans*-2-eicosenoic and *cis*-2-eicosenoic strongly inhibit PtpA, whereas *trans*-11-eicosenoic acid only slightly inhibits PtpA. All measurements were performed twice and data were normalized to the control *E. coli* lysate. $IC_{50}$ values of PtpA inhibition by *trans*-2, *cis*-2 and *trans*-11 eicosenoic acid were calculated with the Prism 7 software (GraphPad) and it was revealed that the $IC_{50}$ values were 11.26, 8.20 and 27.97 µM for *trans*-2, *cis*-2 and *trans*-11-eicosenoic fatty acid, respectively. ESA, Eicosenoic Fatty Acid.

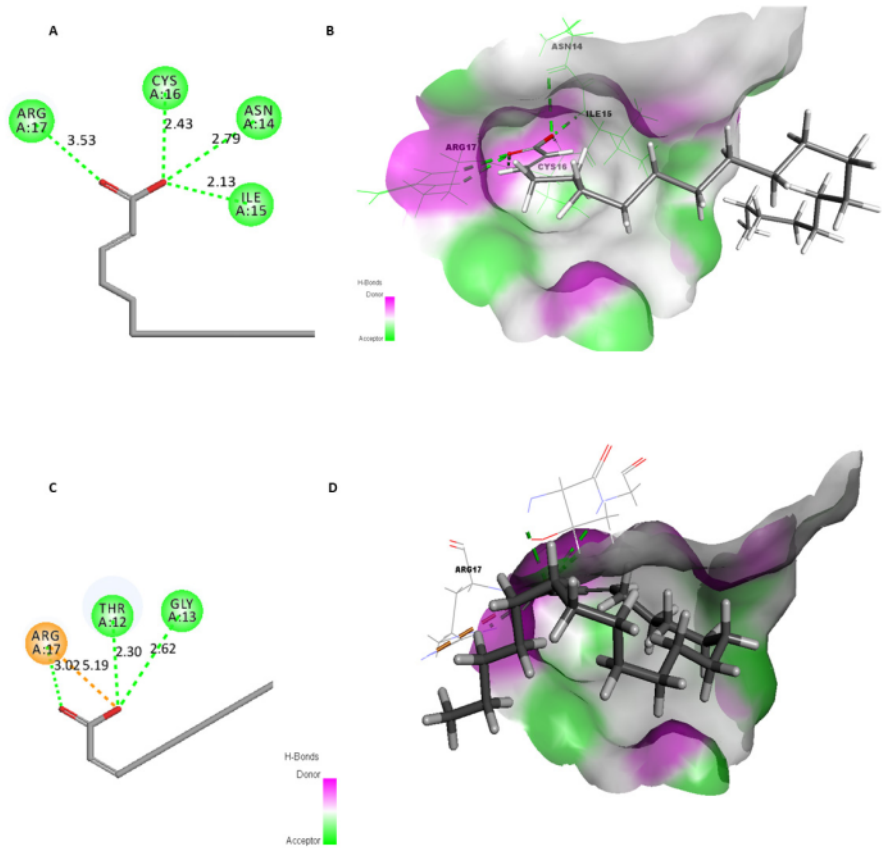


**Figure 3. A and B: Docking analysis of PtpA inhibition by *cis*-2-eicosenoic acid. Four amino acid residues of PtpA are in close proximity to the *cis*-2-eicosenoic acid. C and D: Docking analysis of PtpA inhibition with *trans*-2-eicosenoic acid. Three amino acids are in close proximity to *trans*-2-eicosenoic acid.**

**Table 1. Energy and binding interaction of co-crystalized Mtb PtpA (1U2Q) with eicosenoic fatty acids**

| Compound | cDocker energy (kcal/mol) | Binding interaction (amino acid residue) |
|---|---|---|
| *cis*-2-eicosenoic acid | –37,1939 | $Asn_{14}$, $Ile_{15}$, $Cys_{16}$, $Arg_{17}$ |
| *trans*-2-eicosenoic acid | –33,0076 | $Thr_{12}$, $Gly_{13}$, $Arg_{17}$ |
| *trans*-11-eicosenoic acid | –28,3423 | $Gly_{13}$, $His_{49}$ |

phenyl phosphate (pNPP). The released *para*-nitrophenol gave a typical yellow colour of reaction mixture which is measured spectrophotometrically at 410 nm (Chiaradia *et al.*, 2008).

**Inhibition of PtpA with eicosenoic fatty acids**. Inhibition of PtpA by *trans*-2 and *cis*-2-eicosenoic acids is shown in Fig. 2. It is shown that the *trans*-2 eicosenoic acid, and to a higher extent the *cis*-2-eicosenoic acid, are capable of inhibiting PtpA.

**Docking analysis**. Interaction study of PtpA with the *cis*-2-eicosenoic acid is depicted in Fig. 3. The fatty acid shows interaction with four amino acid residues of PtpA, i.e. $Asn_{14}$, $Ile_{15}$, $Cys_{16}$ and $Arg_{17}$ with binding energy of -37.1939 kcal/mol. Strong interaction of PtpA is also found with *trans*-2-eicosenoic acid via two potential amino acid residues, i.e. $Thr_{12}$, $Gly_{14}$, and to a lesser degree with $Arg_{17}$. On the other hand, docking of PtpA with *trans*-11-eicosenoic acid reveals it to be prone to have weaker interaction in terms of both the energy and the distance of amino acid residues, which is in agreement with the inhibition assay results. Binding parameters of the tested eicosenoic fatty acids are summarized in Table 1.

## DISCUSSION

The role of phosphatases in the progress of infection has been of interests of many researchers, since these proteins are identified in various bacterial pathogens, such as *Listeria monocytogenes, Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *Streptococcus agalactiae*, *Streptococcus py-*

*ogenes*, *Staphylococcus aureus*, *Salmonella typhimurium*, etc. (Sajid *et al.*, 2015). The study areas could include identification of their host interacting partners and be followed by elucidation of the downstream interferences they cause. The next immediate interest, unsuprisingly, is to find a way to inhibit the secreted bacterial phosphatases, and thus prevent their involvement in the development of infections and diseases.

As TB remains a global concern that belongs to one of the main targets in the Sustainable Development Goal (SGD) in health, prevention of latent TB turns to be one of the focal points in addition to other TB eradication efforts, such as development of new vaccines, novel drugs, as well as improvement of diagnosis. Our current knowledge on roles of mycobacterial phosphatase effectors that are secreted by Mtb into its host's cells enroute its degradation pathway has led researchers to explore inhibitors of Mtb phosphatases. The endeavour to seek new potential inhibitors for Mtb virulence proteins and drugs againts TB is nowadays approached by differents strategies. Among those strategies are direct screening of natural compounds, *in silico* screening of phosphatase inhibitors, and synthesis of novel compounds or modified compounds predicted to be able to inhibit Mtb phosphatases.

The study presented here employs an *in silico* report that has underlined the potential inhibitory effect of *trans*-2-eicosenoic fatty acid on Mtb PtpA (Dhanjal *et al.*, 2014). Our data confirmed for the first time that *trans*-2-eicosenoic fatty acid strongly inhibits PtpA, with an $IC_{50}$ of 11.26 µM. Interestingly, its *cis* isomer (*cis*-2-eicosenoic fatty acid) showed an even stronger inhibition to PtpA, with an $IC_{50}$ of 8.20 µM. The ability of these eicosenoic acids to inhibit PtpA is comparable to the other PtpA potential inhibitors, such as chalcone derivatives (Mascarello *et al.*, 2010; Chiaradia *et al.*, 2012) whose $IC_{50}$ ranging from 8.4 to 53.7 µM, and analogues of natural products stevastelin, roseofilin and prodigiosins, whose $IC_{50}$ values ranging from 8.8 to 28.7 µM (Manger *et al.*, 2005). In contrast, the *trans*-11-eicosenoic acid isomer of those compounds showed a much higher $IC_{50}$ value, i.e. 27.97 µM and only slightly inhibited PtpA (Fig. 2). The fact that both *trans*-2 and *cis*-2 eicosenoic acids strongly inhibit PtpA, whereas *trans*-11 does not, shows that the double bond position contributes more to the inhibitory effect of the eicosenoic acids than its *cis* or *trans* stereochemistry (Fig. 2). It is somehow surprising that a small molecule such as eicosenoic acid, rather than complex inhibitors as many researchers have reported, strongly interacts with PtpA.

## CONCLUSIONS

These findings show that both, the *cis*-2 and *trans*-2-eicosenoic fatty acids are potential candidates for PtpA inhibitors. A further study is deemed necessary in order to investigate whether these compounds bind specifically to the Mtb's phosphatase by comparing their inhibitory effects on human phosphatases. Additionally, it is also important to employ an assay to prove whether these compounds are capable of preventing Mtb latent infection *in vivo*.

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## Conflicts of Interest

All authors declare no conflict of interest.

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