

Supplementary Materials: Bulgecin A: The Key to a Broad-Spectrum Inhibitor That Targets Lytic Transglycosylases

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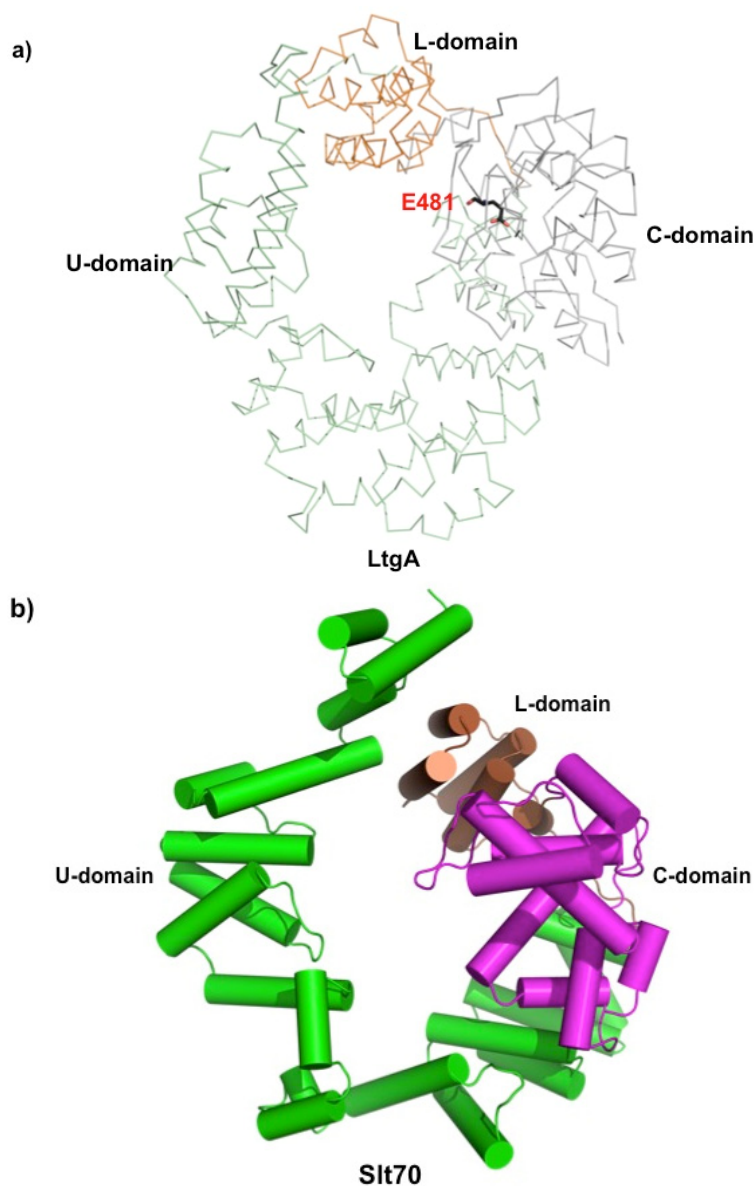


Figure S1. (a) Ribbon model of LtgA highlighting the conserved U (green), L (orange) and C (grey) domains. The catalytic residue of LtgA E481 is shown in black; (b) Secondary structure of Slt70. The domain organization of LtgA represented by cylinders is close to Slt70, the soluble lytic transglycosylase from *E. coli*.

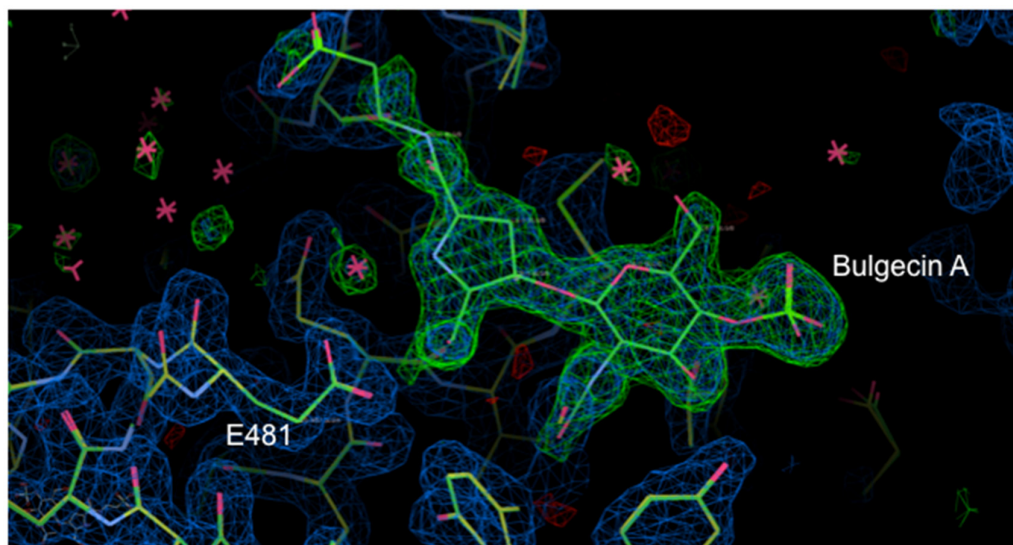


Figure S2. The final F_o-F_c electron density map of bulgecin A contoured at 3 sigma. The final $2F_o-F_c$ map of LtgA contoured at 2 sigma.

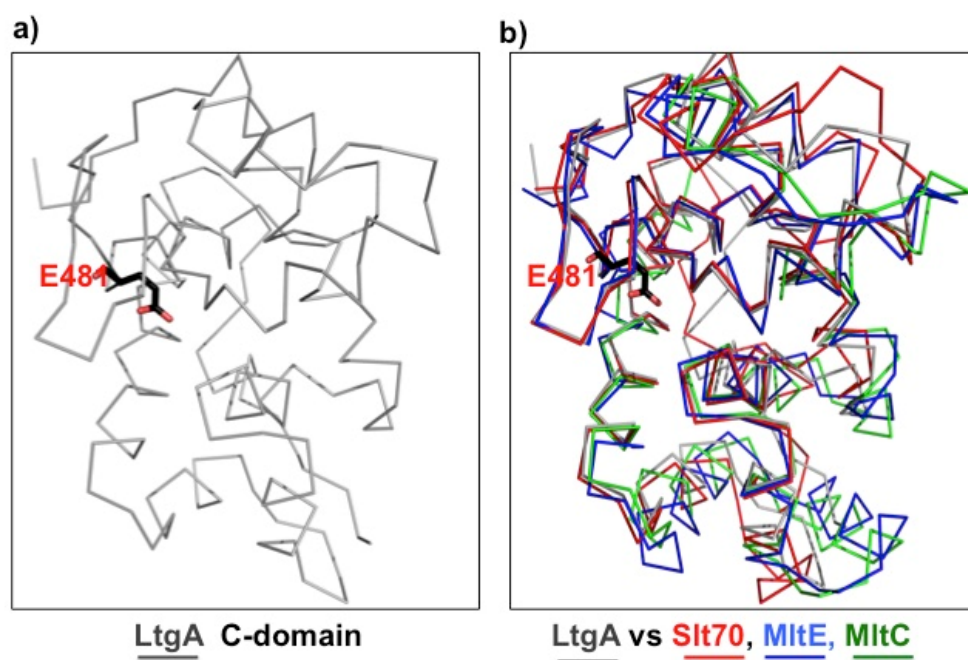


Figure S3. The catalytic domain of lytic transglycosylases is highly conserved. (a) Ribbon model of the catalytic domain of LtgA; (b) The catalytic domain of LtgA is aligned to Slt70, MltE, and MltC; all lytic transglycosylases from *E. coli*.

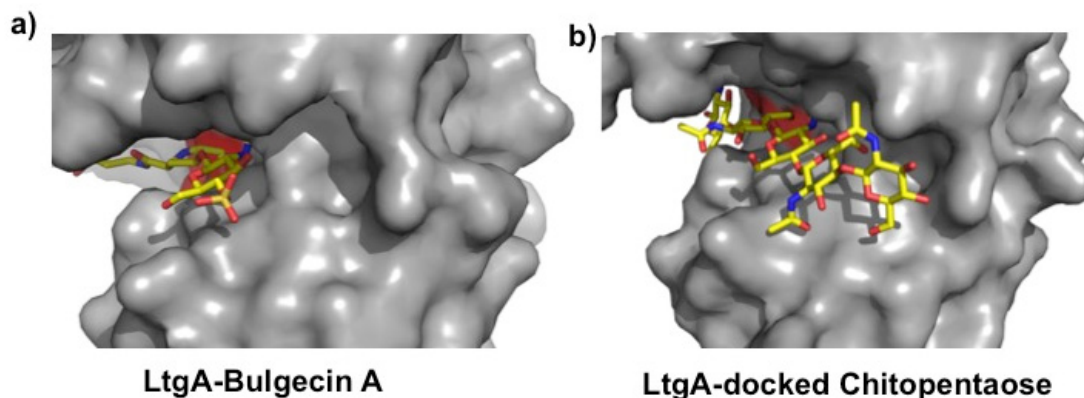


Figure S4. Bulgecin A occupies the active site of LtgA. **(a)** Surface model of the interaction between LtgA and bulgecin A. The model highlights the active site groove with bound bulgecin A. The catalytic residues are colored in red; **(b)** Surface model of docked chitopentaose in the active site groove of LtgA. Chitopentaose mimics the PG glycan strand.

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Slt70 -----AFNNQWDLVQATIAGKLWDHLEERFPLAYNDLFKRYTSGKEIPQSYAMAIAR 476
LtgA  LTAQTAFDHGFYDMVNSAERTDRKLNLYTLRYISPFKDTVIRHAQNVNVDPAWVYGLIR 479
      ** . : : : : : : . . . * : : * : : : : : : : *

↓
Slt70  L--JAWNPKVKSPVGASGLMQIMPGTATHTVKMFSIPGYSSPGQLLPETNINIGTSYLQY 536
LtgA  QESRFVMGAQSRVGAQGLMQVMPATAREIAGKIGM---DAAQLYTADGNIRMGTWYMAD 535
      *** : . : * *** : : : : : * . . . : : . : ** : * : : * :

Slt70  VYQQFGNNRIFSSAAYNAGPGRVRTLGNLSAGRIDAVAFVESIPFSETRGVVKNVLAYDA 596
LtgA  TKRRLQNNVLAAGYNAGPGRARRWQADT--PLEGAVYAETIPFSETRDYVKKVMANAA 593
      . : : * : : : : * : : : : * * . : : : : * : : : : * : : *

Slt70  YYRYFMGDKPTLMSATEWGRRY-- 618
LtgA  YYASLFGAPIPLKQ-RMGIVPAR 616
      ** : : * . . . *

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Figure S5. Sequence alignment of the C-domain of LtgA and Slt70. Residues predicted to be involved in glycan chain binding and/or catalysis are highlighted in red and those that are involved in PG stem peptide interactions are highlighted in blue.



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