

# Application of genome-scale stoichiometric model of *Vibrio vulnificus* CMCP6 for *in silico* drug targeting

Hyun Uk Kim<sup>1</sup>, Tae Yong Kim<sup>1</sup>, Kwangjoon Jeong<sup>3</sup>, Soo Young Kim<sup>3</sup>, Joon Haeng Rhee<sup>3</sup>, Sang  
Yup Lee<sup>1,2\*</sup>

1. Department of Chemical and Biomolecular Engineering (BK21 Program), Metabolic and Biomolecular Engineering National Research Laboratory, Center for Systems and Synthetic Biotechnology, Institute for the BioCentury, Korea Advanced Institute of Science and Technology, Daejeon 305-701, Republic of Korea
  2. Department of Bio and Brain Engineering, BioProcess Engineering Research Center and Bioinformatics Research Center, Korea Advanced Institute of Science and Technology, Daejeon 305-701, Republic of Korea
  3. Clinical Vaccine R&D center, Chonnam National University Medical School, Kwangju 501-746, Republic of Korea
- \*email: [leesy@kaist.ac.kr](mailto:leesy@kaist.ac.kr)

## Abstract

*Vibrio vulnificus* is a halophilic and highly human-pathogenic bacterium, showing very high mortality rate when infected [1]. In order to facilitate the drug development process for this, we undertook *in silico* analysis to identify specific drug targets in the genome-scale metabolism of *V. vulnificus*. With a newly sequenced and annotated genome of *V. vulnificus*, we first reconstructed its genome-scale metabolic network consisting of 946 reactions and 766 metabolites (Table 1). Subsequently, we employed constraints-based flux analysis [2], an optimization-based simulation technique, to validate the model in comparison with experimental data, and identify essential genes comprising the metabolic network. Essential genes herein refer to genes responsible for the specific enzymatic reactions whose deletions result in the failure of biomass formation.

In order to identify primary drug targets, we applied constraints-based flux analysis to the genome-scale model of *V. vulnificus* with maximization of biomass as an objective function under random media. Here, the random media indicate a set of media covering all possible combinations of carbon and nitrogen sources so as to account for various nutrients available for the pathogens inside the human body. In this study, the random media consist of 22 carbon sources and 41 nitrogen sources, and the simulation was performed for each combination. Uptake of sulfate, phosphate and oxygen was allowed in all cases. As a result, 228 enzymatic reactions were identified as primary drug targets.

These candidate gene targets still need to be subjected to further *in silico* analyses in order to narrow them down. For this, various drug targeting approaches could be employed, and a common set of enzyme targets obtained from these approaches as well as constraints-based flux analysis approach above can be collected, which will likely to

reduce the number of target candidates. Finally, it is necessary to compare the sequence of enzyme targets with the human genome sequence using BLAST to exclude candidates that might cause side-effects in the human body. This study demonstrates that drug targeting using *in silico* approaches facilitates not only the systems-level analysis of the bacterial metabolism, but also a rational design of experiments applicable to biomedical science.

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Table 1: Features of the genome and the *in silico* genome-scale stoichiometric model of *V. vulnificus* CMCP6.

Features	Number
<b>Genome feature</b>	
Genome size (base pairs, bp)	5,126,798
No. of open reading frames (ORFs)	4,796
<b><i>In silico</i> metabolic model</b>	
No. of reactions (redundant) included in the model	946
No. of biochemical reactions	810
No. of transport reactions	136
No. of metabolites	766
No. of ORFs assigned in metabolic network	669

## References

1. Gulig, P.A., Bourdage, K.L. & Starks, A.M. Molecular Pathogenesis of *Vibrio vulnificus*. *J Microbiol* **43 Spec No**, 118-131 (2005).
2. Price, N.D., Reed, J.L. & Palsson, B.O. Genome-scale models of microbial cells: evaluating the consequences of constraints. *Nat Rev Microbiol* **2**, 886-897 (2004).