High-Throughput Screen for Novel Antimicrobials using a Whole Animal Infection Model

Terence I. Moy†,‡,§, Annie L. Conery‡,§, Jonah Larkins-Ford‡,§, Gang Wu‡,§, Ralph Mazitschek¶, Gabriele Casadei_, Kim Lewis_, Anne E. Carpenter_, and Frederick M. Ausubel†,‡,§,*

†Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, ‡Department of Molecular Biology, §Center for Computational and Integrative Biology, and ¶Center for Systems Biology, Massachusetts General Hospital, Boston, Massachusetts 02114, _Department of Biology, Northeastern University, Boston, Massachusetts 02115, and _Imaging Platform, Broad Institute of MIT and Harvard, Cambridge, Massachusetts 02142

ABSTRACT The nematode *Caenorhabditis elegans* is a unique whole animal model system for identifying small molecules with *in vivo* antiinfective properties. *C. elegans* can be infected with a broad range of human pathogens, including *Enterococcus faecalis*, an important human nosocomial pathogen. Here, we describe an automated, high-throughput screen of 37,200 compounds and natural product extracts for those that enhance survival of *C. elegans* infected with *E. faecalis*. Using a robot to dispense live, infected animals into 384-well plates and automated microscopy and image analysis, we identified 28 compounds and extracts not previously reported to have antimicrobial properties, including six structural classes that cure infected *C. elegans* animals but do not affect the growth of the pathogen *in vitro*, thus acting by a mechanism of action distinct from antibiotics currently in clinical use.