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A female *Aedes aegypti* mosquito attempts to take flight after a blood meal. The complete sequencing of this disease vector is reported on page 1718, with an accompanying Perspective on page 1703.

Photo: James Gathany/CDC

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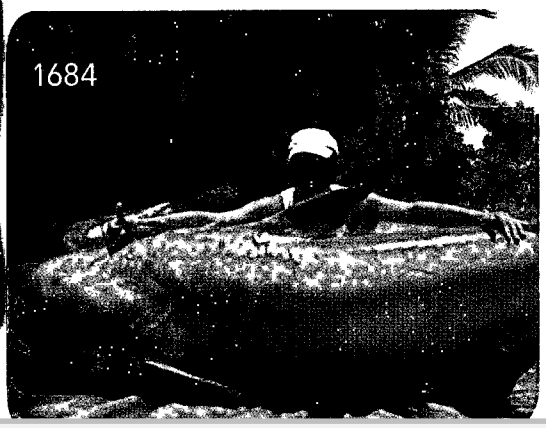

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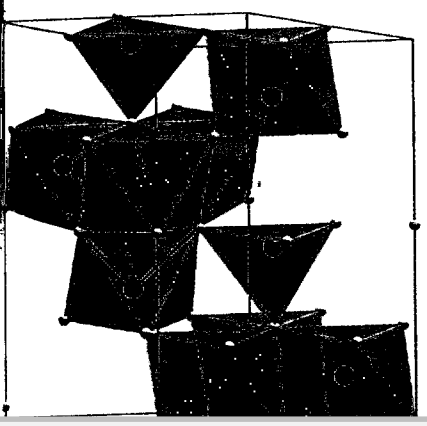

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An Antifungal Agent Inhibits an Aminoacyl-tRNA Synthetase by Trapping tRNA in the Editing Site

Fernando L. Rock,[1]* Weimin Mao,[1]* Anya Yaremchuk,[2,3] Mikhail Tukalo,[2,3] Thibaut Crépin,[2] Huchen Zhou,[1,4] Yong-Kang Zhang,[1] Vincent Hernandez,[1] Tsutomu Akama,[1] Stephen J. Baker,[1] Jacob J. Plattner,[1] Lucy Shapiro,[5] Susan A. Martinis,[6] Stephen J. Benkovic,[7] Stephen Cusack,[2] M. R. K. Alley[1]†

Aminoacyl–transfer RNA (tRNA) synthetases, which catalyze the attachment of the correct amino acid to its corresponding tRNA during translation of the genetic code, are proven antimicrobial drug targets. We show that the broad-spectrum antifungal 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690), in development for the treatment of onychomycosis, inhibits yeast cytoplasmic leucyl-tRNA synthetase by formation of a stable $tRNA^{Leu}$-AN2690 adduct in the editing site of the enzyme. Adduct formation is mediated through the boron atom of AN2690 and the 2′- and 3′-oxygen atoms of tRNA's 3′-terminal adenosine. The trapping of enzyme-bound $tRNA^{Leu}$ in the editing site prevents catalytic turnover, thus inhibiting synthesis of leucyl-$tRNA^{Leu}$ and consequentially blocking protein synthesis. This result establishes the editing site as a bona fide target for aminoacyl-tRNA synthetase inhibitors.

Aminoacyl-tRNA synthetases (AARSs) perform a pivotal role in translating the genetic code by catalyzing the attachment of the correct amino acid to its cognate tRNA (*1*). The aminoacylation reaction occurs in two steps: the formation of an enzyme-bound aminoacyl-adenylate, followed by transfer of this activated amino acid to either the 2′- or 3′-hydroxy group on the 3′-terminal adenosine of tRNA. The accuracy of the tRNA aminoacylation reaction is critical to ensuring the fidelity of the genetic code (*2*). To achieve this accuracy, many AARS enzymes possess a proofreading (editing) mechanism that hydrolyzes tRNAs aminoacylated with the incorrect amino acid (*3*). Leucyl-tRNA synthetase (LeuRS) is a proofreading AARS, which possesses distinct synthetic (aminoacylation) and editing active sites separated by more than 30 Å (*4*, *5*). We show that 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690) inhibits LeuRS by trapping $tRNA^{Leu}$ in the editing active site.

AN2690 is a member of a new class of broad-spectrum antifungals (table S1), the benzoxaboroles, which have an unusual chemical attribute: a boron atom (*6*). We isolated spontaneous and ethyl-methanesulfonate (EMS)–induced AN2690-resistant mutants in the yeast *Saccharomyces cerevisiae* (*7*). These genetically dominant mutants were 32- to 512-fold more resistant to AN2690 than the parental *S. cerevisiae* strain (table S2), and their resistance mutations were found to lie in the *CDC60* gene, which encodes the cytoplasmic LeuRS (Cdc60p). Furthermore, all AN2690-resistant mutations mapped to the editing domain (Fig. 1A and table S2) and all but two, $Cys^{326} \rightarrow Arg^{326}$ (C326R) and $Cys^{326} \rightarrow Phe^{326}$ (C326F) (*8*), to the two highly conserved regions that form the editing active site of LeuRS (*9*). Four mutations lie in the threonine-rich region, a locus known in bacterial LeuRS homologs to be involved in binding and hydrolyzing mischarged tRNAs (*9*–*12*). Seven of the nine mutants exhibited an editing defect based on their sensitivity to the structurally related noncognate amino acid norvaline (fig. S1). These results suggest that the editing pocket of Cdc60p is the binding site for AN2690.

To delineate its mode of action, we investigated the effect of AN2690 on the ability of LeuRS to hydrolyze mischarged $tRNA^{Leu}$. Addition of AN2690 to the posttransfer editing assay inhibited the hydrolysis of Ile-$tRNA^{Leu}$ in a dose-dependent manner (Fig. 1B). In addition, we found that AN2690 inhibited tRNA aminoacylation (fig. S2A), and, as would be expected for a LeuRS inhibitor, it blocked protein synthesis in vivo (fig. S2B). Initial aminoacylation experiments also revealed that AN2690 required the presence of tRNA for effective inhibition of aminoacylation activity. Kinetic analysis of aminoacylation inhibition showed that AN2690 acted as a noncompetitive inhibitor with respect to both adenosine triphosphate (ATP) and leucine (fig. S3, A and B). Analysis of the noncompetitive nature of AN2690 revealed that the inhibition constant (K_i) decreased on increasing AN2690's incubation time with tRNA and Cdc60p, before initiating the aminoacylation reaction with ATP. When enzyme and tRNA were incubated with AN2690 for 2 min, the K_i was 31.4 ± 2.8 (SEM) μM, whereas after a 20-min incubation the K_i decreased to 1.85 ± 0.1 μM (fig. S3). To better understand this process, we measured inhibition of aminoacylation as a function of incubation time and AN2690 concentration (Fig. 2A). We found a direct linear relationship between the observed rates of inactivation (k_{obs}) and AN2690 concentrations, with no apparent plateau even at the highest concentration tested (fig. S4). From these data, we deduced a rate of inactivation of the enzyme ($k_{inactivation}$) of 0.66 ± 0.10 min^{-1}

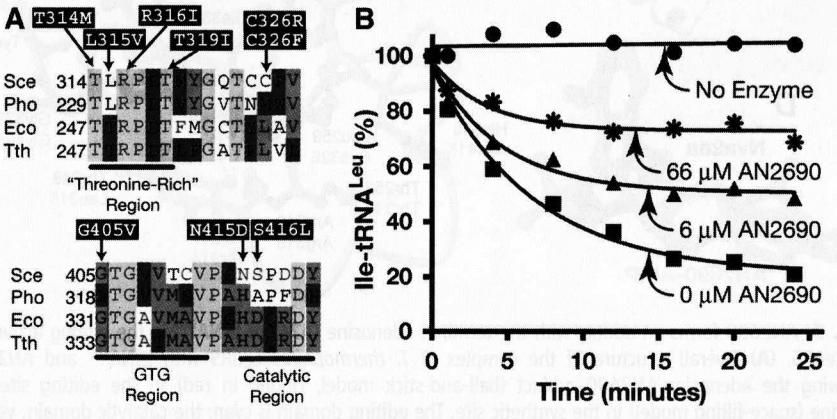

Fig. 1. (**A**) *S. cerevisiae* AN2690 resistance mutations in the editing active site of Cdc60p (*8*). Alignment of the conserved regions of the LeuRS editing domains from *S. cerevisiae* (Sce) from CAA97865, *Pyrococcus horikoshii* (Pho) from O58698, *Escherichia coli* (Eco) from AAC73743, and *T. thermophilus* (Tth) from BAD69984. The amino acid substitutions that confer resistance in *S. cerevisiae* to AN2690 are in black (table S2). (**B**) AN2690 inhibits posttransfer editing. Deacylation of total brewer's yeast tRNA mischarged with isoleucine, no enzyme control (circles), enzyme control

[1]Anacor Pharmaceuticals, Incorporated, 1060 East Meadow Circle, Palo Alto, CA 94303, USA. [2]European Molecular Biology Laboratory, Grenoble Outstation 6 rue Jules Horowitz, BP181, 38042 Grenoble Cedex 9, France. [3]Institute of Molecular Biology and Genetics, National Academy of Science (NAS) of Ukraine, 252627 Kiev, 3143, Ukraine. [4]School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China. [5]Department of Developmental Biology, Beckman Center, Stanford University School of Medicine, Stanford, CA 94305, USA. [6]Department of Biochemistry, University of Illinois, Urbana, IL 61801–3732, USA. [7]Department of Chemistry, Pennsylvania State University, University Park, PA 16802, USA.

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