IN BRIEF

PUBLIC HEALTH

Defeating dengue with *Wolbachia*

The introduction of *Wolbachia* bacteria into *Aedes aegypti* mosquitoes confers resistance to dengue virus (DENV) and other arboviruses, and the release of *Wolbachia*-infected mosquitoes in endemic regions may be an effective arboviral control strategy. Now, Utarini et al. report the results a cluster-randomized trial involving the release of *A. aegypti* mosquitoes infected with the wMel strain of *Wolbachia pipiensis* for the control of DENV infections in Yogyakarta, Indonesia. Geographical clusters randomly received either deployments of wMel-infected *A. aegypti* (interventional clusters) or no deployments (control clusters), and virologically confirmed dengue (VCD) was surveyed in 8,144 patients from 18 primary care clinics. In the control clusters, VCD occurred in 9.4% of patients but remarkably DENV was detected in only 2.3% of patients in interventional clusters. The incidence of symptomatic dengue fever and hospitalizations for VCD was significantly reduced in interventional clusters, suggesting that mosquito deployments could eliminate dengue fever in endemic regions.

ORIGINAL ARTICLE Utarini, A. et al. Efficacy of *Wolbachia*-infected mosquito deployments for the control of dengue. *N. Engl. J. Med.* **384**, 2177–2186 (2021)

VIRAL EVOLUTION

Searching for relatives of SARS-CoV-2 in bats

Coronaviruses (CoVs) that are close relatives of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been found in bats and pangolins, yet the evolutionary history of SARS-CoV-2 is unclear. Zhou et al. report the discovery of bat CoVs from Yunnan province, China, that are closely related to SARS-CoV-2, including a virus that displays high sequence identity to SARS-CoV-2 in most genomic regions. The authors performed metagenomic sequencing on 411 bat samples and assembled 24 CoV metagenomes, including four SARS-CoV-2-related viruses. The closest relative to SARS-CoV-2 was *Rhinolophus pusillus* virus RPYN06, which has 94.5% sequence identity and, in some genes, has the highest similarity to SARS-CoV-2 identified thus far. However, the spike gene has a much lower sequence identity, suggestive of a genomic recombination event, making RPYN06 the second closest relative of SARS-CoV-2 identified to date after the bat CoV RaTG13, highlighting the potentially complex evolutionary history of SARS-CoV-2.

ORIGINAL ARTICLE Zhou, H. et al. Identification of novel bat coronaviruses sheds light on the evolutionary origins of SARS-CoV-2 and related viruses. *Cell* <https://doi.org/10.1016/j.cell.2021.06.008> (2021)

CELLULAR MICROBIOLOGY

Evolution of a viral nucleocapsid

Evolutionary theory on the origin of viruses suggests that primordial replicators recruited host proteins for virion formation. In a recent study, Tetter et al. evolved a bacterial enzyme that does not have an inherent affinity for nucleic acids into a virus-like nucleocapsid protein that efficiently packages and encapsidates copies of its own mRNA. Starting with the multimeric cage-forming protein lumazine synthase from *Aquifex aeolicus*, the authors performed a series of evolutionary experiments leading to the artificial nucleocapsid. Cryo-electron microscopy of the evolutionary intermediates and the final design revealed a structural evolution towards a virus-like architecture through protomer reorganization. Furthermore, evolution led to highly specific virus-like RNA packaging mediated by secondary RNA stem-loop structures, and protection from external nucleases.

ORIGINAL ARTICLE Tetter, S. et al. Evolution of a virus-like architecture and packaging mechanism in a repurposed bacterial protein. *Science* **372**, 1220–1224 (2021)

SYNTHETIC BIOLOGY

Designer bacteria

Engineering bacteria by removing sense codons and their cognate tRNAs could lead to the creation of cells with desirable properties for biotechnology applications, such as complete resistance to contaminating phages or the ability to incorporate noncanonical amino acids (ncAAs) during translation, resulting in the synthesis of novel non-natural heteropolymers. Previous work led to the creation of a strain of *Escherichia coli* (Syn61) with a synthetic recoded genome in which two sense codons (serine TCG and TCA) and the amber stop codon TGA were replaced with synonymous codons, such that Syn61 uses only 61 of the 64 available codons. In a recent study, Chin and colleagues evolved Syn61 and removed the tRNAs and the translation release factor that decode the TCG, TCA and TAG codons, leading to complete resistance to a cocktail of phages and the encoded incorporation of ncAAs during ribosome-mediated biosynthesis.

The authors hypothesized that replacement of TCG, TCA and TAG codons in the Syn61 genome would enable the deletion of tRNA^{Ser}_{CGA}, tRNA^{Ser}_{UGA} and release factor 1 (RF1) that decode these codons. Deletion of genes that encode these tRNAs and RF1 led to the creation of a new strain (Syn61Δ3), confirming that these genes could be deleted; however, the strain experienced growth defects. Through random parallel mutagenesis and selection, the authors created a Syn61Δ3 variant that grew significantly faster.

Next, the authors investigated how tRNA and RF1 deletion affected phage infection, which relies on the cell decoding the canonical genetic

code of viral genomes. Cells were treated with a cocktail of phages containing the phages lambda, P1vir, T4, T6 and T7, which have TCA or TCG sense codons that are 10–58 times more abundant than the TAG codon in their genomes, and observed that cells lacking tRNA^{Ser}_{CGA} and tRNA^{Ser}_{UGA} (but not RF1 alone) were resistant to phage-induced lysis, suggesting that the deletion of those tRNAs confers resistance to a broad range of phages.

The authors also demonstrated how assigning ncAAs to TCG, TCA and TAG in Syn61Δ3 could be used to incorporate ncAAs at specific sites in biopolymers. Using tyrosyl-tRNA synthetase–tRNA and pyrrolysyl-tRNA synthetase–tRNA pairs, the authors were able to reassign the TCG, TCA and TAG codons for specific ncAA incorporation into biopolymers. Two different ncAAs were incorporated at three different locations, and three distinct ncAAs were simultaneously incorporated into a ribosome-produced biopolymer in Syn61Δ3 cells. Furthermore, the authors were able to encode the synthesis of noncanonical hexamers and octamers as protein fusions, as well as the synthesis of a non-natural macrocycle that resembles the products of non-ribosomal peptide synthetases.

This study highlights the potential of sense codon reassignment in bacteria to generate phage-resistant strains and designer proteins with a range of applications.

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ORIGINAL ARTICLE Robertson, W. E. et al. Sense codon reassignment enables viral resistance and encoded polymer synthesis. *Science* **372**, 1057–1062 (2021)

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