lack of detectable resistance to cilagicin is likely linked to its ability to bind both C55-PP and C55-P, because changes to two distinct molecular targets must evolve for resistance to develop. The binding to multiple targets may be an important consideration when developing future antibiotics.

The same research team also recently used their synBNP approach to overcome colistin resistance (*5*). Resistance to colistin, another lipopeptide antibiotic, raised substantial concern when a resistance determinant encoded by a gene called *mcr-1* (mobilized colistin resistance 1) spread rapidly in pathogenic enteric bacteria around the globe. Widespread dissemination of the *mcr-1* gene jeopardized the utility of colistin as the last line of defense against infections caused by MDR Gram-negative bacteria (*12*). Gram-negative bacteria have a cell wall that is encased by an additional lipid outer membrane, which is a permeability barrier to many small molecules. This limits the number of antibiotics in our anti-Gram-negative arsenal that target the cell wall or other targets within. Colistin has potent antibiotic activity against Gram-negative bacteria because it binds to lipopolysaccharides and phospholipids in the outer membrane, displacing divalent cations, which disrupts membrane integrity and ultimately leads to cell death (*13*, *14*).

Wang *et al.* (*5*) set out to identify BGCs that encoded the production of colistin analogs, with the clever rationale that nature may have figured out how to diversify the antibiotic to overcome resistance. Like their work with cilagicin, the authors focused their attention on a single BGC and synthesized its predicted product, which they named macolacin, which possessed antibacterial activity against colistin-resistant bacteria. The authors were able to further improve macolacin activity by optimizing its lipid moiety (see the figure), which facilitates interaction with the membrane. One improved derivative, biphenyl-macolacin, outperformed the parent molecule and possessed potent in vitro activity against intrinsically colistin-resistant *Neisseria gonorrhoeae,* and carbapenem-resistant and extensively drug-resistant *Acinetobacter baumannii,* which are recognized as urgent threats by the CDC (*7*).

Although cilagicin and macolacin showed promising in vitro activity against problematic MDR bacterial pathogens, the real question was how well do these agents perform in an infection model? The answer will dictate the future of these agents as therapeutics. In both studies, Wang *et al.* (*4, 5*) assessed each of these compounds in a mouse infection model. For cilagicin, there was an initial setback. High levels of serum binding to cilagicin blocked its antibacterial activity. The authors overcame this hurdle by altering the lipid component of cilagicin, ultimately utilizing the same biphenyl moiety used to improve macolacin, as a strategy to reduce serum binding. Such hit-to-lead optimization is a key feature in antibiotic development (*15*). The new structure, cilagicin-BP (see the figure), was as efficacious as vancomycin when used to treat mice infected with MDR *S. aureus* and even more so when used to treat *Streptococcus pyogenes* infection (which is not MDR). The efficacy of biphenyl-macolacin was also evaluated in mice infected with either carbapenem-resistant *A. baumannii* engineered to express the *mcr-1* colistin resistance gene, or an *mcr-1*–expressing clinical isolate of *A. baumannii* that is resistant to all antibiotics tested. Treatment with colistin did not reduce the bacterial load beyond that used to establish the infection, whereas treatment with biphenyl-macolacin reduced the bacterial load by five orders of magnitude.

Many promising antibiotic compounds fall by the wayside because of low production titer during microbial fermentation. Aside from a rare handful of compounds, chemical synthesis is ultimately used to produce the quantity, and notably, the chemical diversity of analogs necessary to define the clinical potential of a lead pharmacophore. In two studies, Wang *et al.* not only produced two new biologically inspired antibiotics but established a route for their synthesis and generation of analogs. The next major steps for their development are absorption, distribution, metabolism, excretion, and toxicity studies, which may reveal the need for further structural optimization before entry into clinical trials. Although clinical deployment of cilagicin and macolacin may take time, Wang *et al.* (*4*, *5*) have established an inspirational interdisciplinary roadmap for future antibiotic discovery that may tip the scales in our fight against antimicrobial resistance. ■

REFERENCES AND NOTES

1. D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **83**, 770 (2020).
2. P. A. Hoskisson, R. F. Seipke, *mBio* **11**, e02642 (2020).
3. L. L. Ling *et al.*, *Nature* **517**, 455 (2015).
4. Z. Wang *et al.*, *Science* **376**, 991 (2022).
5. Z. Wang *et al.*, *Nature* **601**, 606 (2022).
6. I. W. Hamley, *Chem. Commun.* **51**, 8574 (2015).
7. Centers for Disease Control and Prevention, "Antibiotic Resistance Threats in the United States, 2019" (2019); www.cdc.gov/drugresistance/biggest-threats.html.
8. K. Kitano A. Tomasz, *Antimicrob. Agents Chemother.* **16**, 838 (1979).
9. M. A. T. Blaskovich *et al.*, *ACS Infect. Dis.* **4**, 715 (2018).
10. K. J. Stone, J. L. Strominger, *Proc. Natl. Acad. Sci. U.S.A.* **68**, 3223 (1971).
11. T. Schneider *et al.*, *Antimicrob. Agents Chemother.* **53**, 1610 (2009).
12. Y.-Y. Liu *et al.*, *Lancet Infect. Dis.* **16**, 161 (2016).
13. M. Schindler, M. J. Osborn, *Biochemistry* **18**, 4425 (1979).
14. A. Sabnis *et al.*, *eLife* **10**, e65836 (2021).
15. M. Miethke *et al.*, *Nat. Rev. Chem.* **5**, 726 (2021).

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EVOLUTION

How full is the evolutionary fuel tank?

A meta-analysis quantifies the heritable genetic variance in fitness—the fuel of evolution

By **Bruce Walsh**

In 1898, Hermon Bumpus gathered 136 house sparrows immobilized by an ice storm, noting that the averages of several morphological traits differed between survivors and nonsurvivors. This was one of the first attempts to measure the phenotypic selection component of Charles Darwin's thesis, that adaptation is driven by heritable traits that affect fitness. Since then, a vast literature on quantifying associations between trait values and fitness has emerged (*1*). The quantification of Darwin's second evolution component—that such traits are heritable—required the development of quantitative genetics by Ronald Fisher in 1918 (*2*). Although the selection and genetics components can be combined to determine the expected change in any trait, of greater interest is the general adaptive potential of a population. On page 1012 of this issue, Bonnet *et al.* (*3*) present a meta-analysis of 19 studies showing the abundance of heritable variations in fitness and the potential for adaptation.

Fisher famously stated that "natural selection is not evolution," meaning that if a trait is not heritable, no amount of selection will result in a change in the offspring of surviving parents. Fisher's key to deciphering heritability was noting that parents pass along specific variants of a gene (alleles), rather than entire genotypes, to their offspring. The sum of all the single-allele effects for a given trait carried by an individual is defined as their breeding value (BV) for that trait. BVs are best understood in terms of deviations from the mean, so that a random individual has an expected BV of zero, which implies that its offspring will, on average, be average. The expected deviation of an offspring from the population

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mean is simply the average of the BVs of its parents. As a result, parents with exceptional BVs have offspring that, on average, deviate substantially from the population mean. Conversely, offspring from parents with modest BVs fall close to the mean.

The spread of individual BVs is a measure of the evolutionary potential of a trait. This is the basis of the additive variance of a trait, defined as the variance among BVs for that trait in a given population. If this variance is small, offspring have very little resemblance to their parents, whereas if it is large, exceptional parents tend to have exceptional offspring. If there is no additive variance for a trait, it will not evolve. More generally, if there is no additive variance in fitness, no trait will genetically respond to selection.

South African meerkats (*Suricata suricatta*) were among the populations examined by Bonnet *et al.*, who used the total number of pups in a mother's lifetime as the measure of her reproductive fitness.

PHOTO: ROBIN HOSKYNS/MINDEN PICTURES

Thus, one of the holy grails in evolutionary genetics is to estimate the additive variation in fitness itself, which gives a general measure of the evolutionary potential of a population and places limits on the maximal response for any trait. This challenging estimation problem was tackled by Bonnet *et al.* using a collection of 19 long-term vertebrate population studies (covering a total of 561 cohorts and ~250,000 individuals) from North America, Europe, Africa, and Oceania. The meta-analysis showcases an immense, but doable, effort in estimating this fundamental evolutionary parameter.

Bonnet *et al.* used total number of offspring, also known as lifetime reproductive success (LRS), as the measure for the fitness of an individual. The LRS parameter is converted to relative fitness simply by dividing LRS for an individual by the average LRS of the population, which allows for quantifiable comparisons across studies. In statistical terms, if a population shows a significant additive variance in fitness among its individuals, this implies that parents with higher LRSs than the population average also have a high BV for LRS, and thus their children also tend to have high LRSs.

Estimating BVs, and thus additive variance, is a common problem in modern animal breeding, built around using pedigree information. A BV exists even when the trait is not displayed, as it is a measure of how exceptional an offspring from that parent would be, if produced. In the case of milk production, information on the BV of a bull is provided by the observed yields of his mother, sisters, and daughters. The same pedigree machinery used by breeders can, in theory, be applied in natural populations to estimate the additive variance of any measured trait. Pedigrees for natural populations can be constructed using molecular markers, and closed populations of vertebrates are well suited for such analyses. Even with perfect pedigrees, the transition of pedigree methods from a large and well-structured domesticated population to a small wild population has been somewhat rocky (*4*). Domesticated pedigrees tend to be much deeper and denser than those for natural populations, resulting in greater precision in BV estimates. Furthermore, fitness is a problematic trait for standard pedigree methods, which assume trait values are continuous and follow a Gaussian distribution, whereas fitness data are highly discrete—a parent can only have an integer number of offspring, with a large point mass at zero, that is, individuals with zero offspring. Although there have been a few attempts to estimate the additive variance in fitness in wild populations using standard pedigree methods, the failure of the Gaussian assumption suggests that these are likely rather biased.

Bonnet *et al.* extended these pedigree methods by using a discrete Poisson distribution with an inflated zero value instead of a Gaussian and provided a much better fit for the fitness data. Using the improved fitting, their resulting average estimate of the additive variance in relative fitness, $V_A(w)$, was two- to fourfold larger than previous values. To put it in a more tangible context, this means that if the fitness of a population drops by a third, it would take roughly 10 generations to recover back to normal fitness levels. Hence, populations with shorter generation times might have a better chance to somewhat mitigate anthropogenic changes.

In nature, the target of selection is almost certainly a constantly shifting, high-dimensional (i.e., multi-trait) phenotype that may poorly project onto individual traits or even a set of traits. Most studies of adaptation are structured around some assumed edifice of traits that affects fitness. A poor choice of traits can give a misleading impression of population adaptation. Fortunately, an estimate of $V_A(w)$ provides an upper bound, and therefore a maximal possible change in any trait independent of selection. For example, a typical trait heritability of 0.3 will mean that 30% of the trait variation is due to variance in BVs, and the maximal possible change in the average value of a trait in the population is about one standard deviation every four generations. A more reliable way to estimate $V_A(w)$ can help to better quantify the nature of selection and the robustness of a population to major environmental changes. ■

REFERENCES AND NOTES

1. B. Walsh, M. Lynch, *Evolution and Selection of Quantitative Traits* (Oxford Univ. Press, 2018).
2. M. Lynch, B. Walsh, *Genetics and Analysis of Quantitative Traits* (Sinauer, 1998).
3. T. Bonnet *et al.*, *Science* **376**, 1012 (2022).
4. J. D. Hadfield, A. J. Wilson, D. Garant, B. C. Sheldon, L. E. B. Kruuk, *Am. Nat.* **175**, 116 (2010).

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