

are those that focus on compounds that counter tumour proliferation *in vitro*⁶: the glutarimide compounds cycloheximide and lactimidomycin. Both of these inhibit protein synthesis by the 80S ribosome, but not by the 70S ribosome. The researchers' crystal structures identify the binding site for each compound at the exit of the peptidyl transferase centre. Comparisons with data for 70S structures⁷ show that the prokaryotic ribosome has components that occlude the glutarimide binding pocket, explaining these compounds' selectivity.

The authors' biochemical data also help to rationalize the different effects of each compound. Cycloheximide binds its ribosome pocket at any time during translation and blocks the exit of ribosome substrates from the peptidyl transferase centre. But the rate at which lactimidomycin binds its binding pocket is much lower than that of the substrates — so it cannot be accommodated in the ribosome during protein translation, but can bind and block the process before it starts. Because lactimidomycin is larger than cycloheximide, the authors propose that its binding is slower because of the extra effort needed to accommodate its greater bulk. In other words, when comparing the mechanism of action of the two compounds, size really does matter!

The inhibitor-bound structures reported by

Garreau de Loubresse and colleagues are by no means the end of the road to understanding the selectivity and mechanism of action of drugs that target ribosomes. For example, because these structures lack both messenger RNA and transfer RNA, it remains to be seen how compounds such as edeine and cryptopleurine — which inhibit ribosome activity by interacting with mRNA and/or tRNA — affect protein translation at the ribosome.

As techniques for studying the ribosome improve, there will undoubtedly be quantum leaps in our understanding of how these machines work and in our ability to modulate their activity. Indeed, such a breakthrough⁸ was made earlier this year when cryoelectron microscopy (cryoEM) was used to visualize the 80S ribosome from the malaria-causing protozoan *Plasmodium falciparum* bound to the translation inhibitor emetine, at a resolution of 3.2 ångströms. This demonstrated that cryoEM can achieve sufficiently high resolution to distinguish the details of electrostatic-bond formation between ribosomes and bound compounds. Unlike X-ray crystallography, cryoEM does not need crystals⁹, so the ability to use cryoEM removes a major hurdle to structural studies of ribosomes.

In the meantime, by successfully clearing this hurdle, Garreau de Loubresse *et al.* have

delivered groundbreaking data at atomic resolution that should further our understanding of how a diverse set of compounds affects the function of the 80s ribosome. It will be interesting to see which technique — X-ray crystallography or cryoEM — delivers the first 55S ribosome structure in the presence of an inhibitor. ■

Nelson B. Olivier is in the *Innovative Medicines and Early Development Unit, AstraZeneca Pharmaceuticals, Cambridge Science Park, Cambridge CB4 0FZ, UK.*
e-mail: nelson.olivier@astrazeneca.com

1. Garreau de Loubresse, N. *et al. Nature* **513**, 517–522 (2014).
2. Wilson, D. N. *Crit. Rev. Biochem. Mol. Biol.* **44**, 393–433 (2009).
3. Wimberley, B. T. *Curr. Opin. Invest. Drugs* **10**, 750–765 (2009).
4. Perez-Fernandez, D. *et al. Nature Commun.* **5**, 3112; <http://dx.doi.org/10.1038/ncomms4112> (2014).
5. Taguchi, A. *et al. ChemMedChem* <http://dx.doi.org/10.1002/cmdc.201402208> (2014).
6. Schneider-Poetsch, T. *et al. Nature Chem. Biol.* **6**, 209–217 (2010).
7. Schuwirth, B. S. *et al. Science* **310**, 827–834 (2005).
8. Wong, W. *et al. eLife* **3**, e03080 (2014).
9. Bai, X., Fernandez, I. S., McMullan, G. & Scheres, S. H. *eLife* **2**, e00461 (2013).

This article was published online on 10 September 2014.

NEIL LOSIN



BIODIVERSITY

Leaping lizards

Loss of biodiversity is a hallmark of the human-dominated era, but our influence can also alter the processes that generate biodiversity. On page 543 of this issue, Helmus *et al.* study human-assisted movement of lizards around Caribbean islands, and show that a major geographic parameter of a classic theory of biodiversity has been replaced by an economic one (M. R. Helmus, D. L. Mahler and J. B. Losos *Nature* **513**, 543–546; 2014).

The theory of island biogeography predicts that biodiversity is greatest on large and less-isolated islands (or other discrete habitat fragments), but the underlying processes of speciation and long-distance colonization are usually too slow for the theory to be tested directly.

The shipping trade has speeded things up for anole lizards in the Caribbean, transporting them around the islands as stowaways (pictured: *Anolis equestris*). The authors find that the resulting diversity of *Anolis* species fits theoretical predictions about island size, but that economic isolation — such as occurred on Cuba during the cold war — has overtaken geographic isolation as the other key factor. **Patrick Goymer**