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► **COVER:** 'Question marks' by George Marshall, inspired by the Review on p736.



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**F**or microbiologists who work on multiprotein complexes, progress towards understanding how they function at the molecular level can seem slow. Structural information for each component is vital, but generating high-quality data can be the rate-limiting step, especially if the complex of interest spans a membrane. Bacterial secretion systems, which can cross one, two or even three membranes, are therefore particularly challenging systems to work on. However, researchers working on type IV secretion systems (T4SSs) received a boost earlier this year with the determination of the cryo-electron microscopy structure of a T4SS core complex. On page 703, Remi Fronzes, Peter Christie and Gabriel Waksman discuss the progress that has been made in the structural biology of T4SSs over the past decade and review the mechanistic insights that have been gained. Structural data can of course be important in many areas of microbiology, and on page 724 Tilman Schirmer and Urs Jenal review the latest structural data for the protein families involved in bis-(3'-5')-cyclic dimeric GMP (c-di-GMP) signalling, and their functional implications.

Structural data can provide crucial insights into the molecular mechanisms underlying cellular processes, but to maximize the impact of these insights the system being studied must be genetically tractable. *Leptospira* spp. were identified as the causative agent of leptospirosis over 100 years ago, but our understanding of this neglected disease has been greatly hindered by the fact that, until recently, these organisms could not be manipulated genetically. On page 736, Mathieu Picardeau and colleagues review the progress that has been made in our understanding of the life cycle and pathogenicity of *Leptospira* spp. since the publication of the first genome sequence 6 years ago allowed the development of tools for genetic analysis.

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