Writing the macrocycle manual

New computational and biochemical tools and informatic rules should spur research on a relatively underexplored class of molecules.

Macrocycles come in a variety of shapes and sizes, including carbonaceous polyketides, ribosomal and nonribosomal peptides, chemically crosslinked conjugates and knotted miniproteins. Because macrocycles are larger in surface area than the small molecules typically used in drug discovery efforts, they have been viewed as a panacea to tackle the ‘undruggable’ targets that have defied synthetic strategies. Yet challenges in designing and making macrocycles, much less understanding their pharmacokinetic properties, have simultaneously dissuaded some scientists from studying these molecules. For those fainthearted, we offer hope in this issue in the form of three research articles reporting on the hows and whys of macrocycle development.

Some may be skeptical that macrocycles are underexplored given that, as noted by Heinis, ~70 macrocycles are currently in use as drugs (News & Views, p. 696). Yet Heinis also points out that most of these compounds, such as the antibiotics erythromycin and vancomycin and the immunosuppressant cyclosporin, are either natural products or directly derived from them, suggesting the ability to create new therapeutically meaningful macrocycles remains limited. So what’s the problem? At the 2012 SciBX Innovation in Drug Discovery and Development Summit on macrocycles and constrained peptides, panel members highlighted four outstanding unknowns that have stymied macrocycle development (SciBX, doi:10.1038/scibx.2012.1176), three of which focused on the behavior of macrocycles in cells and organisms—specifically, their pharmacokinetics, cell permeability and oral bioavailability—whereas the last highlighted the need for more information about how macrocycles interact with their targets.

The report from Villar et al. (Article, p. 723) begins with a compelling example of this final unknown: In their search for all nonredundant co-crystal structures of proteins with orally available macrocycle drugs, the authors identify only 22 such structures in the PDB. By quantifying these structures, however, the authors are able to propose a set of guidelines for physicochemical properties such as molecular weight, numbers of hydrogen bond donors and acceptors, and partition coefficients that can be used to enable further macrocycle discovery. Additionally, the authors describe the hot spots on proteins used by macrocycles as compared to those used by small molecules, helping to elucidate which targets are suited to which type of ligand. Further tests of these proposals and refinement of the guidelines will require the engagement of crystallographers to elucidate structures of known macrocycle-protein complexes in addition to more general efforts to identify and validate new macrocycle drugs.

Gavenonis et al. (Article, p. 716) take a different approach to parse likely targets, building from the concepts of hot spots and peptide-binding grooves in their comprehensive survey of the PDB to identify ‘hot loops’ that energetically anchor protein-protein interactions. In their analysis, the authors identify several examples where loop-derived peptides have already been found that bind with high affinity and specificity to their expected target, confirming the utility of the approach. The list of 1,407 hot loops, including 364 loops using nonconsecutive hot spots that would be difficult to access using more traditional strategies, should serve as an immediate entry point to develop ligands against targets of interest. Peptide chemists can help to identify general strategies by which loops can be converted into ligands. But how can sufficient macrocycles be made to test these hypotheses?

Enter butelase-1, the fastest peptide ligase known, reported by Nguyen et al. (Article, p. 732). Previous work has developed a suite of possible cyclization methods, ranging from the wholly synthetic (Nat. Chem. Biol. 8, 358–365, 2012) to the split-intein mediated (Nat. Chem. Biol. 5, 655–663, 2009) to the ribosomal incorporation of non-natural amino acids that spontaneously form cyclized products (Nat. Chem. Biol. 5, 888–890, 2009), along with other creative solutions. However, butelase-1 fills a unique gap with its ability to cyclize a diversity of peptide substrates in nearly quantitative yields and short reaction times. Enzymologists will be able to help determine why this enzyme is so efficient and whether there might be other related enzymes hiding in plain sight that could similarly serve as facile tools for macrocycle construction.

Although each of these papers points to new opportunities in macrocycle research, it is also clear that the ‘macrocycle instruction manual’ remains incomplete. Chemical biologists are particularly suited to contribute new insights, techniques and tools to fill the pages. At Nature Chemical Biology, we welcome submissions describing innovative methodologies to make macrocycles or reporting mechanistic insights into macrocycle biosynthesis, such as the description of how Baeyer-Villiger monooxygenases turn ketones into carbonates (Nat. Chem. Biol. 10, 552–554, 2014) or the discovery that fungal biosynthetic clusters—lacking the thioesterase domains that cyclize natural products in bacteria—use condensation-like domains for this reaction (Nat. Chem. Biol. 8, 823–830, 2012).

We also seek submissions that use macrocycles as tools, whether as part of a drug discovery campaign or to uncover basic biological insights, such as deciphering the mechanism of lasso peptide recognition by a siderophore receptor (Nat. Chem. Biol. 10, 340–342, 2014). Within drug discovery efforts, as with studies focused on small molecules, we prioritize manuscripts that describe new techniques for discovering molecules of interest, including the tris-(bromomethyl) benzene anchoring of phage-displayed peptides (Nat. Chem. Biol. 5, 502–507, 2009), as well as submissions that identify new mechanisms of engagement on known targets, such as pyridomycin’s insertion into both cofactor and substrate binding pockets of the antituberculosis target enoyl reductase (Nat. Chem. Biol. 10, 96–98, 2014). Of course, we encourage submissions of papers that deliver on the promise of macrocycles’ ability to unlock new portions of ‘undruggable’ space, exemplified by the unexpected ‘sterol sponge’ mechanism of amphotericin (Nat. Chem. Biol. 10, 400–406, 2014). We are mindful that issues such as cellular permeability and uptake are ongoing challenges for macrocycle research in general, and for peptides in particular, and so consider the strengths of each manuscript within this context.

As Nick Terrett, chief scientific officer of Ensemble Therapeutics, indicated during the SciBX summit, “there’s been a lot of buzz about macrocycles being really special molecules, and some clearly are, but most of them are not.” We look forward to future discoveries of those special macrocycles that enhance scientific understanding and therapeutic capabilities.