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Dark chemistry

Ultra-large libraries of virtual molecules help researchers to explore the chemical universe — and point to potential drugs.

Drug discovery is a notoriously tough process. Pharmaceutical companies tend to prize efficiency, so many potential lead compounds are merely iterations of what the companies already have, dictated by what they already know, and rely on already exploited molecular scaffolds (the core structure of a molecule).

The need to diversify molecular scaffolds to improve the chances of success in drug discovery has been referred to as escaping from 'flatland' — the reliance on synthetic methods that build flat molecules. Another way to investigate the unexplored potential in the molecular universe is to find a way to reveal what is hidden in the shadows. Some estimates say that there are at least 10^{60} different drug-like molecules: a novemdecillion of possibilities. How, then, to open up more of this dark chemical space?

A paper published this week demonstrates the power of ultra-large virtual libraries in helping researchers to look into the unknown (J. Lyu *et al. Nature* http://doi.org/10.1038/s41586-019-0917-9; 2019). In it, the authors built a virtual library of around 350 million drug-like molecules. They used this to simulate the ways that these molecules could interact with two therapeutically relevant proteins — AmpC β-lactamase, a target for antibiotics, and the D_4 dopamine receptor, linked to several neurological disorders and a member of the pharmacologically important family of G protein-coupled receptors.

After this virtual screening, the team synthesized the top-scoring compounds and tested them against the two targets. One of the compounds turned out to be the most potent inhibitor of AmpC β-lactamase known, and is chemically distinct from all other known inhibitors.

Of the 500 or so molecules the group made that targeted the D_4 dopamine receptor, one had an unprecedented ability to stimulate it. This compound's selectivity over other dopamine receptor types, and its preferential activation of the G protein signalling pathway, are both important properties that might help to minimize unwanted side effects when, and if, it's used as a drug.

Others have already demonstrated the potential of smaller virtual libraries to aid drug design. But as the accompanying News and Views (D. E. Gloriam. *Nature* http://doi.org/10.1038/d41586-019-00145-6; 2019) shows, the increased library size makes an important difference. The publicly available library (http://zinc15.docking.org) is anticipated to increase to more than a billion molecules within two years.

Going from a promising compound to an approved drug is still a tortuous and uncertain process. But by having access to a greater portion of the chemical universe, the chances of discovering a star should be greater too. ■

Gut feeling

The once-radical idea that gut microbes affect mental health is now a major research pursuit.

Just ten years ago, the idea that microorganisms in the human gut could influence the brain was often dismissed as wild. Not any more.

Links between the central nervous system and the trillions of bacteria in the gut — the microbiota — are now a major focus of research, public interest and press coverage. But how does this 'gut–brain axis' work? The mechanisms by which microorganisms shape aspects of brain functioning such as memory and social behaviour, and how they might contribute to conditions such as depression and neurodegenerative disease, are tenuous and often controversial.

Much of what we know so far is based on studies showing correlations between specific gut bacteria, their metabolites and neurological symptoms. But these correlations do not prove cause and effect. Many studies use animal models, which don't accurately mirror human traits or behaviours. Human studies have been limited: they're usually based on relatively small numbers of people, and might not control for a wealth of confounding factors — such as unusual diets, antibiotics or antidepressants — that can affect the microbiota.

A study published this week in *Nature Microbiology* tackles some of these issues (M. Valles-Colomer *et al. Nature Microbiol.* https://doi.org/10.1038/s41564-018-0337-x; 2019). The authors used DNA sequencing to analyse microbiota in the faeces of more than 1,000 people enrolled in Belgium's Flemish Gut Flora Project. The team then correlated different microbial taxa with the participants' quality of life and incidence of depression, using self-reported and physician-supplied diagnoses. The researchers validated the findings in an independent cohort of 1,063 individuals in the Netherlands' LifeLines DEEP project. Finally, they mined the data to generate a catalogue describing the microbiota's capacity to produce or degrade molecules that can interact with the human nervous system.

The researchers found that two groups of bacteria, *Coprococcus* and *Dialister*, were reduced in people with depression. And they saw a positive correlation between quality of life and the potential ability of the gut microbiome to synthesize a breakdown product of the neurotransmitter dopamine, called 3,4-dihydroxyphenylacetic acid. The results are some of the strongest yet to show that a person's microbiota can influence their mental health.

These are still correlations, not causes. Researchers know that the gut microbiota can produce or stimulate the production of neurotransmitters and neuroactive compounds, such as serotonin, GABA and dopamine, and that these compounds can modulate bacterial growth. The challenge now is to find out whether, and how, these microbe-derived molecules can interact with the human central nervous system, and whether that alters a person's behaviour or risk of disease. At least now, answering these questions is a wise pursuit, not a wild one. ■

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