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NEWS IN BRIEF

A snapshot of lead-generation strategies

Most leads originate from known compounds or from high-throughput screens, found a recent report in the *Journal of Medicinal Chemistry* on newly disclosed clinical candidates.

Dean Brown and Jonas Boström, researchers at AstraZeneca, analysed the origins of 66 clinical candidates that were first reported in the *Journal of Medicinal Chemistry* in 2016–2017. They found that 43% of these molecules were derived from previously known compounds, 29% originated from high-throughput screening of large random compound libraries, 14% came from structure-based drug design strategies, 8% came from directed screens of small and well-characterized compound libraries, 5% came from fragment screens and 1% came from DNA-encoded libraries. Some, but not all, of the drugs that originated from known compounds were fast followers.

Few of these new clinical candidates were derived from phenotypic screens, they report. A 2011 analysis in *Nature Reviews Drug Discovery* on the origins of 259 FDA-approved drugs found that target-based screening was the most successful lead-generation strategy for follow-on drugs, whereas phenotypic screening was the most successful approach for first-in-class drugs.

Brown and Boström also assessed the physicochemical properties of hits and their respective candidate drugs, and found that molecular weight was typically the only significant change. Lipophilicity, as measured by cLogP, did not change on average. More than 50% of the clinical candidates were structurally very different, and more complex, than their starting points. But in one case — Gilead Sciences' remdesivir (GS-5734), a nucleoside analogue for the treatment of Ebola — the drug candidate was discovered directly in the screen.

"This study provides a retrospective analysis of past trends which have led to successful clinical candidates, and hopefully proves the framework for the exploitation of future opportunities," the authors write.

Asher Mullard

REVAMPing antibiotic incentives

Members of the US House of Representatives have proposed a bill that would create a much-needed 'pull' incentive, granted upon successful approval of a product, to encourage drug developers to work on antibiotics.

If the REVAMP Act of 2018 passes into law, a drug company that successfully develops priority antimicrobial product will receive a transferable voucher that grants 12 months of exclusive marketing rights to a drug of the firm's choice, to delay market entry of generics in the US. Kevin Outterson, executive director of the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), estimates that this exclusivity extension could be worth more than US$1 billion.

Only ten vouchers will be awarded, and only for antibiotics that are submitted for regulatory review after 1 January 2018.

Antibiotic advocates have been steadily building the case for pull incentives as a means of offsetting the challenging economics of antibiotic development. The Review on Antimicrobial Resistance, commissioned by the UK government and chaired by economist Jim O'Neill, recommended 'market-entry rewards' of $0.8–1.3 billion for new antibiotics in 2016. Earlier this year a final report by DRIVE-AB, an IMI-funded project into the economics of antibiotics, estimated that rewards of $1–1.25 billion could help bring 13–23 truly innovative antibiotics to market in the next 30 years. With the introduction of the REVAMP Act, politicians and funders may be set to heed these calls.

Industry's exodus from antibiotic R&D, meanwhile, continues. In July, Novartis became the latest large pharma company to exit antibacterial and antiviral research. It is laying off 140 employees in the process. "While the science for these programs is compelling, we have decided to prioritize our resources in other areas where we believe we are better positioned to develop innovative medicines that will have a positive impact for patients," the company said in a statement. Novartis's antibiotic pipeline included the phase II β-lactam LYS228, for the treatment of Gram-negative bacteria.

Asher Mullard

FDA approves first marijuana-derived product

The FDA approved GW Research's cannabidiol (CBD) for the treatment of two rare and severe forms of epilepsy, Lennox–Gastaut syndrome and Dravet syndrome. This was the first FDA approval for a drug that contains a purified drug substance derived from marijuana.

"This approval serves as a reminder that advancing sound development programs that properly evaluate active ingredients contained in marijuana can lead to important medical therapies," said FDA commissioner Scott Gottlieb. "We'll continue to support rigorous scientific research on the potential medical uses of marijuana-derived products and work with product developers who are interested in bringing patients safe and effective, high-quality products."

Researchers have previously reported anti-inflammatory, anti-emetic, neuroprotective and anticancer activity with CBD (*Nature Reviews Drug Discovery* **3**, 771–784; 2004). CBD's activity is distinct from the effects of tetrahydrocannabinol (THC), which causes the intoxication and euphoria associated with marijuana.

GW and others are also developing CBD and THC for other indications. Insys Therapeutics has initiated phase III trials of CBD in seizure disorders and infantile spasms, as well as phase II trials in Prader–Willi syndrome. GW is testing its GWP42003 formulation of CBD for schizophrenia and other indications. GW's nabiximols, a combination of CBD and THC, is in phase III trials for neuromuscular spasm and spasticity (and already approved in this setting in many countries in the European Union and elsewhere). And Intec Pharma is trialling a combination of CBD and THC in phase I for pain.

Dronabinol, first approved by the FDA in 1985 for chemotherapy-induced nausea and vomiting, is a synthetic form of THC.

Asher Mullard