IN BRIEF

MALARIA

Identifying antimalarial drug targets

The mechanism of action of most clinically used antimalarial agents remains elusive. Dziekan et al. apply the cellular thermal shift assay combined with mass spectrometry (MS-CETSA) to identify drug targets in *Plasmodium falciparum*. Using parasite lysate and intact infected red blood cells, MS-CETSA accurately detected the known targets of pyrimethamine and E64d and revealed *P. falciparum* purine nucleoside phosphorylase (PfPNP) as a common binding target for the two quinoline drugs, quinine and mefloquine. In vitro biophysical studies combined with X-ray crystallography established high-affinity binding of the compounds in the active site pocket of PfPMP.

ORIGINAL ARTICLE Dziekan, J. M. et al. Identifying purine nucleoside phosphorylase as the target of quinine using cellular thermal shift assay. *Sci. Transl Med.* **11**, eaau3174 (2019)

DRUG DISCOVERY

Role of the Protein Data Bank

The open-access Protein Data Bank (PDB) serves as the single global repository for 3D structural data of proteins, DNA, RNA and their complexes with small molecules. Westbrook and Burley quantitatively assess the impact of the PDB on the discovery and development of 210 new molecular entities (NMEs) approved by the FDA between 2010 and 2016. Analysis of the PDB revealed 5,914 unique structures covering 88% of the NMEs and 86% of their known protein targets. More than half of the 5,914 structures had been deposited in the PDB well before the NME was approved by the FDA. Approximately 10% of worldwide research on the known molecular targets of the 210 NMEs was influenced by structural data from the PDB.

ORIGINAL ARTICLE Westbrook, J. D. & Burley, S. K. How structural biologists and the Protein Data Bank contributed to recent FDA new drug approvals. *Structure* https://doi.org/10.1016/j.str.2018.11.007 (2019)

BIOELECTRONIC MEDICINE

Developing closed-loop neuromodulatory devices

Closed-loop neuromodulation systems aim to treat disease by electrical stimulation of the peripheral nervous system in response to physiological changes. Mickel et al. have now developed a wireless, implantable bio-optoelectronics system, which enables closed-loop optogenetic control of bladder function. The device combines a strain gauge that encircles the bladder to monitor bladder filling and voiding with microscale light-emitting diodes to control inhibitory opsins expressed virally in bladder sensory afferents, wirelessly controlled through a module inserted into the abdomen. The system recognized and attenuated abnormal voiding patterns in cyclophosphamide-induced cystitis in rats. Meanwhile, Zhou et al. describe a wireless artefact-free neuromodulation device capable of closed-loop recording and electrical stimulation on 128 channels, which can detect neural biomarkers and automatically adjust stimulation parameters, for potential applications in neurological disorders. Implantation of the device into the brain of a non-human primate (NHP) enabled long-term recordings of local field potentials, robust detection of neural biomarkers and real-time cancellation of stimulation artefacts. In a closed-loop stimulation experiment in NHPs, the device modulated movement preparatory activity during a delayed-reach task.

ORIGINAL ARTICLES Mickle, A. D. et al. A wireless closed-loop system for optogenetic peripheral neuromodulation. *Nature* https://doi.org/10.1038/s41586-018-0823-6 (2019) | Zhou, A. et al. A wireless and artefact-free 128-channel neuromodulation device for closed-loop stimulation and recording in non-human primates. *Nat. Biomed. Eng.* **3**, 15–26 (2019)

Credit: Jack Walters/Alamy Stock Photo

DRUG DISCOVERY

$GABA_A$ receptor structures solved

$GABA_A$ (γ-aminobutyric acid, type A) receptors are targeted by numerous small-molecule drugs, many of which were discovered before their target was known. Using single particle cryo-electron microscopy (cryo-EM), the first structure of a $GABA_A$ receptor in a physiological conformation, reconstituted into a lipid bilayer, has been solved, as have five structures of the same receptor in complex with various drugs. These structures provide insights into the mechanisms of action of $GABA_A$ receptor-targeting molecules and could provide the basis for future structure-based drug discovery.

The $GABA_A$ receptor modulates phasic and tonic neuronal inhibition. Well-known drugs that target this receptor include the benzodiazepines, which are positive allosteric modulators with sedative, anxiolytic, hypnotic and anticonvulsant properties, but an unknown mechanism of action. Previous work also established that classic benzodiazepines require the presence of specific $GABA_A$ receptor subunits, for unclear reasons.

Masiulis and colleagues solved cryo-EM structures of the $GABA_A$ receptor to resolutions of 3.0–3.7 Å in complexes with the channel blocker picrotoxin (PTX), PTX plus the endogenous ligand γ-aminobutyric acid (GABA), the antagonist bicuculline (BCC), diazepam (a benzodiazepine) plus GABA, and alprazolam (another benzodiazepine) plus GABA. From their PTX work, the authors concluded that this tool compound binds to the open conformation of the channel pore, after which it unexpectedly induces pore closure. GABA binds to this stabilized conformation with lower affinity, thereby explaining how PTX acts as a competitive antagonist of GABA without binding to either of the orthosteric pockets.

Next, the researchers showed that binding of GABA to the orthosteric sites in the $GABA_A$ receptor induces rotation of the extracellular domain, which is reduced in the presence of PTX. Similarly, BCC, which binds to the GABA orthosteric sites, prevents rotation of the extracellular domain and maintains the pore in the closed conformation.

The benzodiazepines bind at an allosteric site between the α and γ subunits. Interestingly, classic benzodiazepines can only modulate $GABA_A$ receptors that contain α1, α2, α3 or α5 subunits. In α4 and α6 subunits, an arginine residue replaces the histidine that interacts with diazepam and alprazolam, leading to steric clashes. Of note, a second binding site for diazepam (but not alprazolam) was observed at intersubunit interfaces within the transmembrane domain and is likely responsible for its anaesthetic properties.

The structures presented in these articles could be used to design $GABA_A$ receptor modulators with particular properties, which could have increased efficacy and safety, and also highlight the emerging opportunities for applying cryo-EM in drug discovery.

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ORIGINAL ARTICLES Masiulis, S. et al. $GABA_A$ receptor signalling mechanisms revealed by structural pharmacology. *Nature* https://doi.org/10.1038/s41586-018-0832-5 (2019) | Laverty, D. et al. Cryo-EM structure of the human α1β3γ2 $GABA_A$ receptor in a lipid bilayer. *Nature* https://doi.org/10.1038/s41586-018-0833-4 (2019)

FURTHER READING Shimada, I. et al. GPCR drug discovery: integrating solution NMR data with crystal and cryo-EM structures. *Nat. Rev. Drug Discov.* **18**, 59–82 (2019)