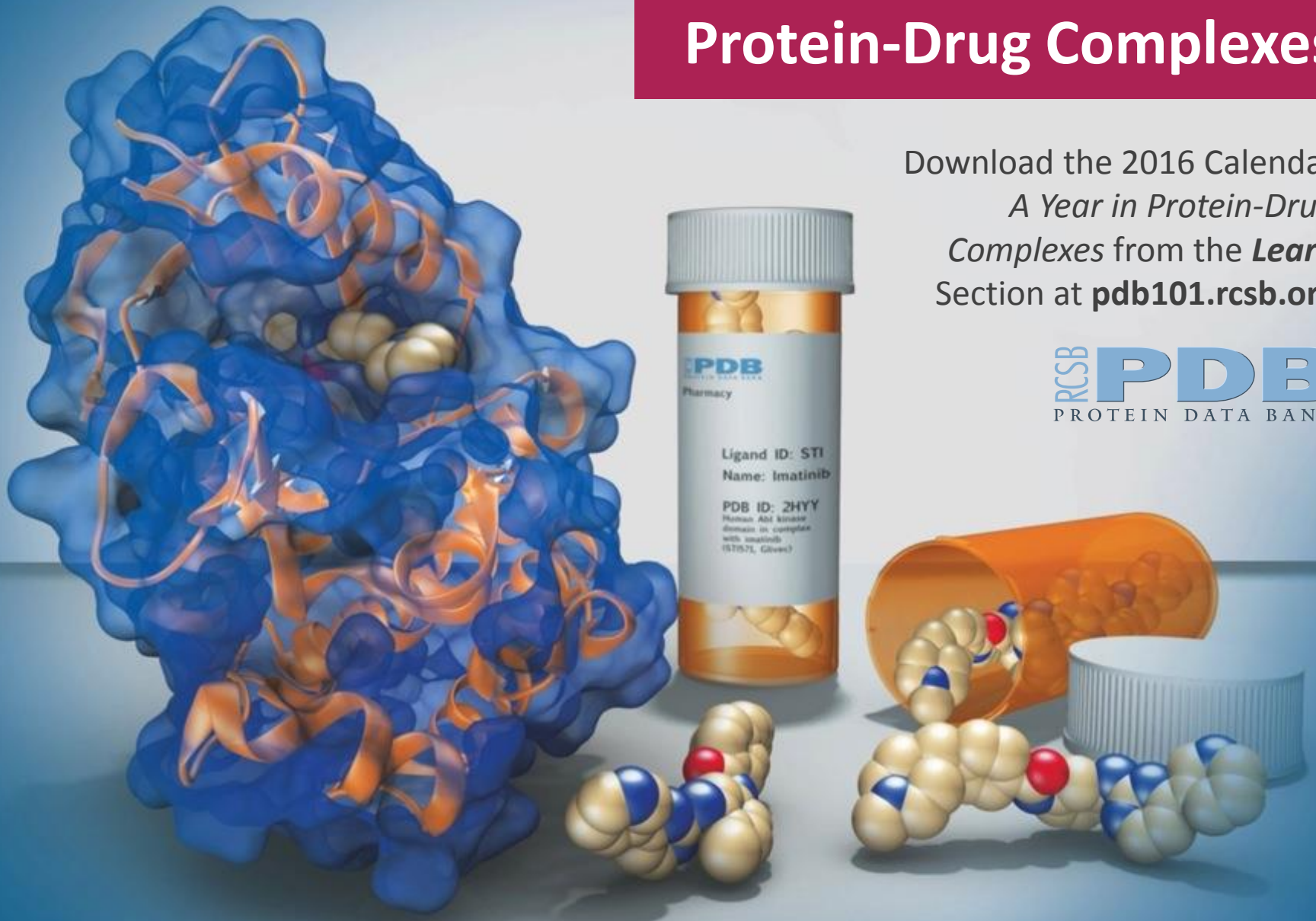
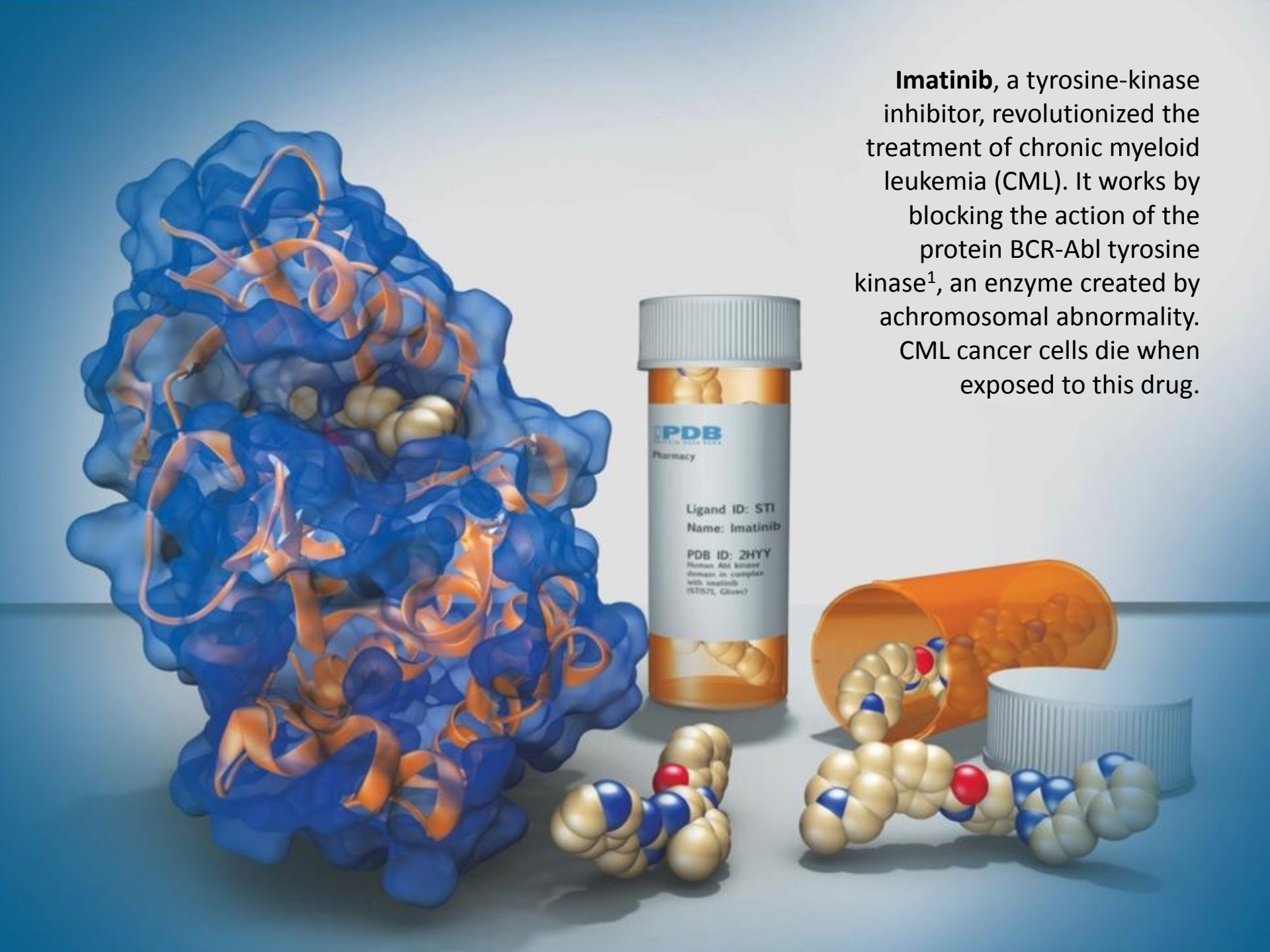
Protein-Drug Complexes

Download the 2016 Calendar *A Year in Protein-Drug Complexes* from the ***Learn*** Section at **pdb101.rcsb.org**

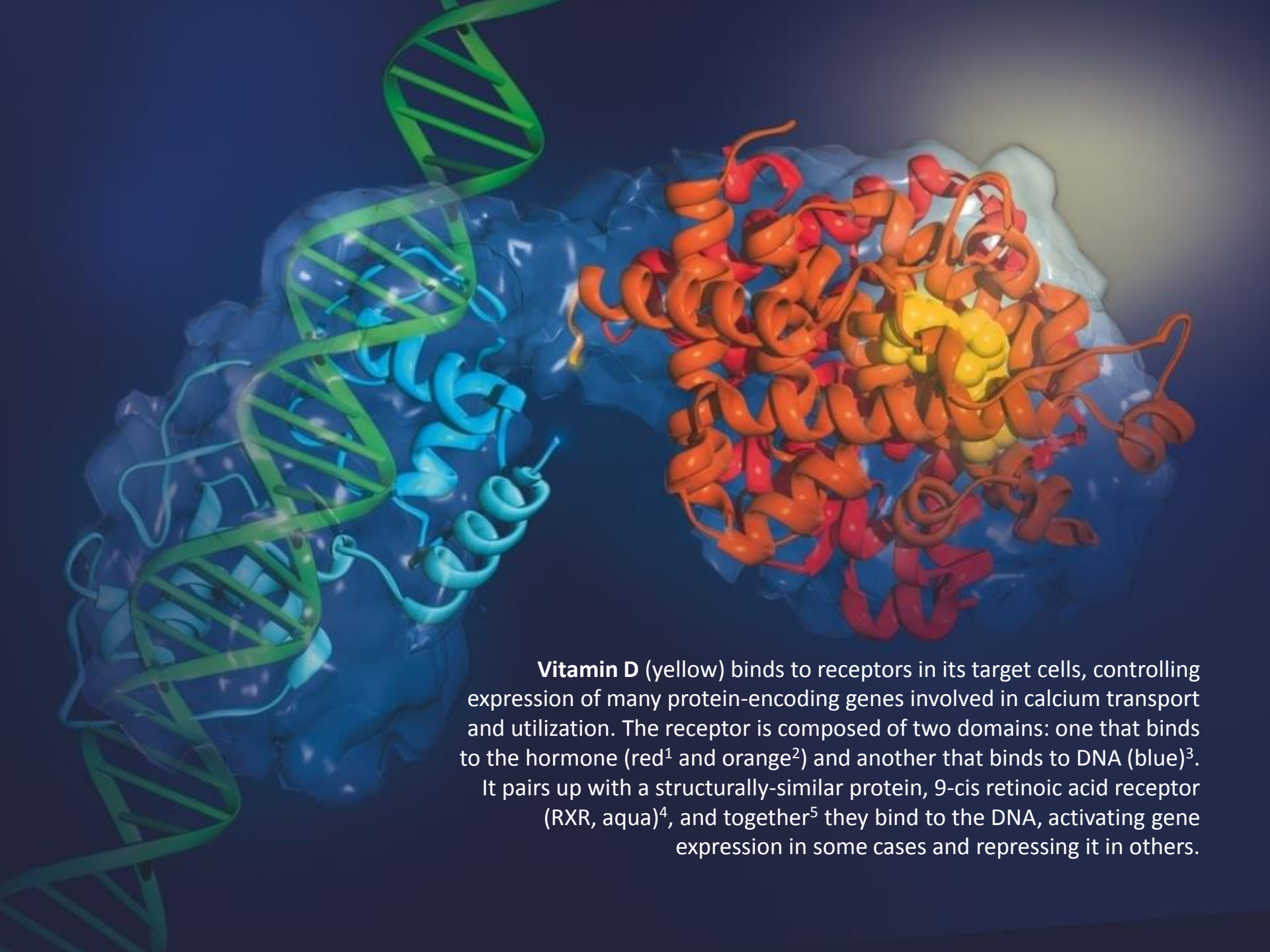
RCSB PDB
PROTEIN DATA BANK



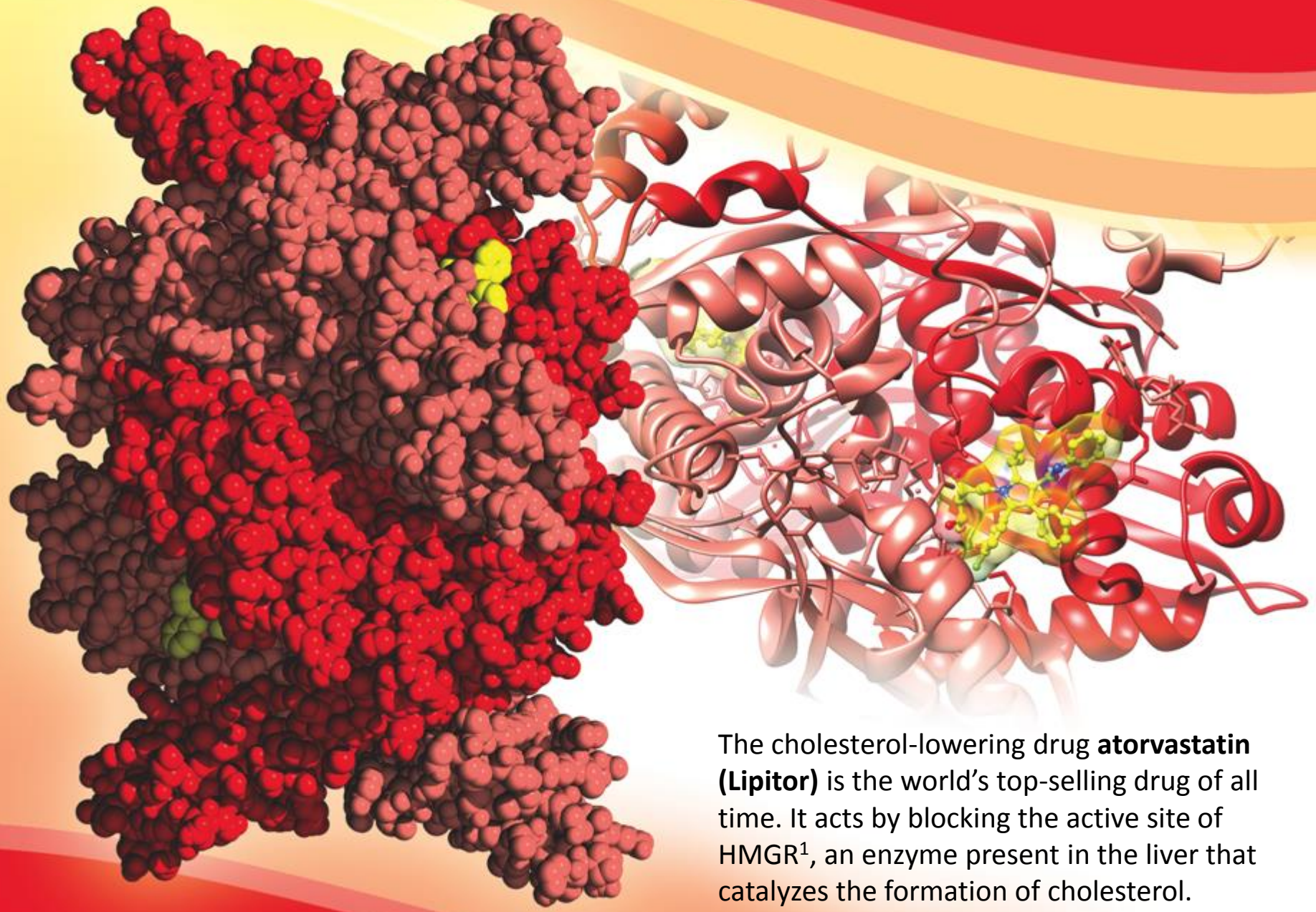
Note: PDB IDs can be found in the notes section of each slide



Imatinib, a tyrosine-kinase inhibitor, revolutionized the treatment of chronic myeloid leukemia (CML). It works by blocking the action of the protein BCR-Abl tyrosine kinase[1], an enzyme created by achromosomal abnormality. CML cancer cells die when exposed to this drug.

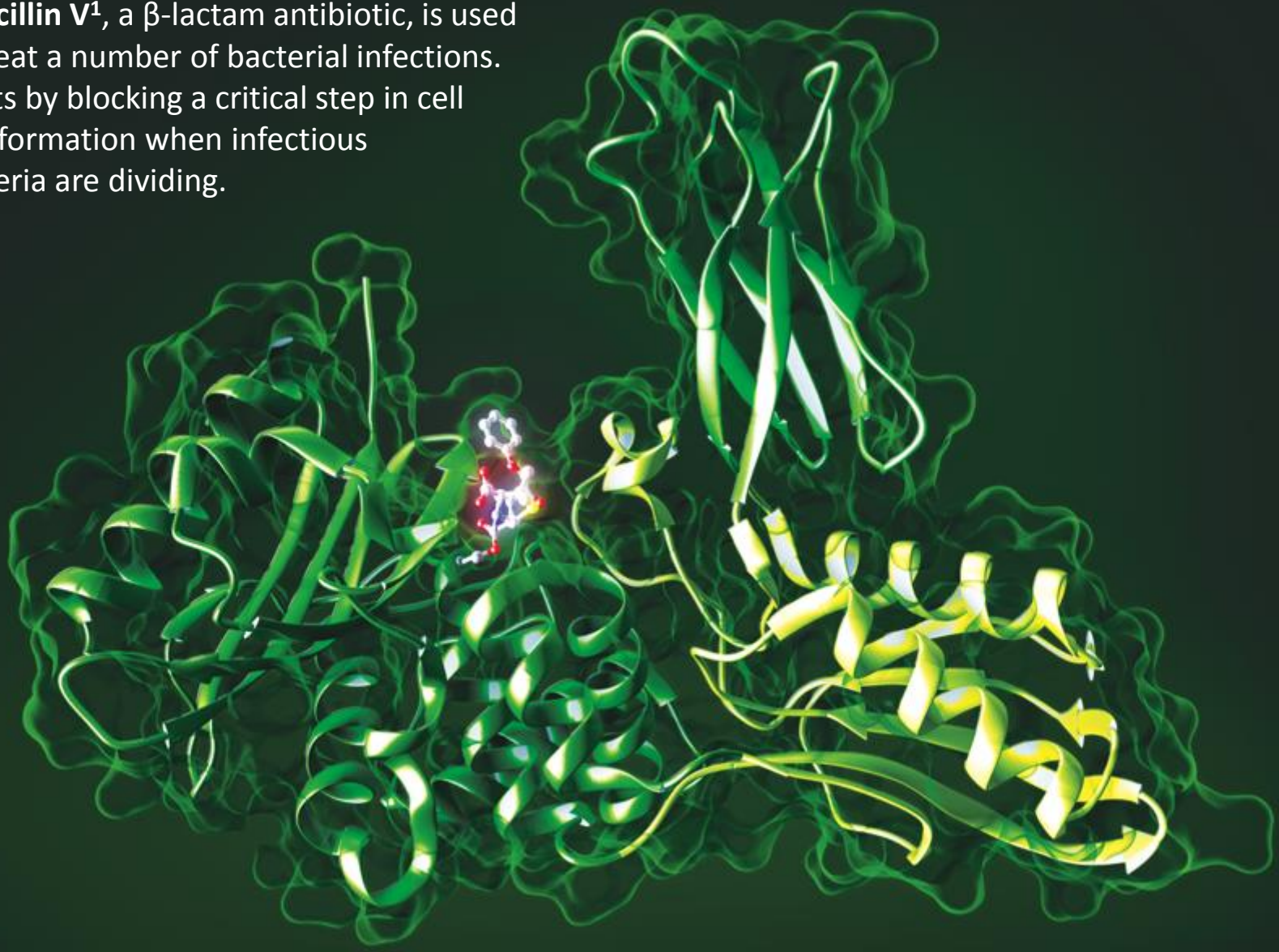


Vitamin D (yellow) binds to receptors in its target cells, controlling expression of many protein-encoding genes involved in calcium transport and utilization. The receptor is composed of two domains: one that binds to the hormone (red[1] and orange[2]) and another that binds to DNA (blue)[3]. It pairs up with a structurally-similar protein, 9-cis retinoic acid receptor (RXR, aqua)[4], and together[5] they bind to the DNA, activating gene expression in some cases and repressing it in others.



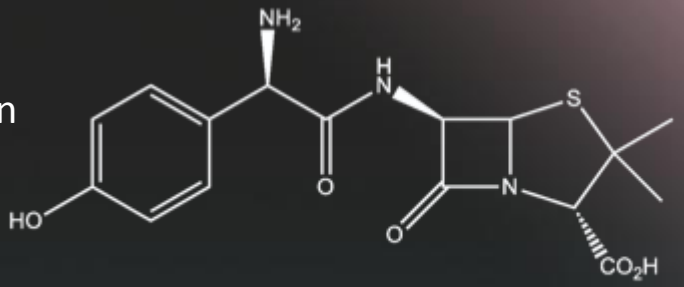
The cholesterol-lowering drug **atorvastatin (Lipitor)** is the world's top-selling drug of all time. It acts by blocking the active site of HMGR[1], an enzyme present in the liver that catalyzes the formation of cholesterol.

Penicillin V[1], a β-lactam antibiotic, is used to treat a number of bacterial infections. It acts by blocking a critical step in cell wall formation when infectious bacteria are dividing.

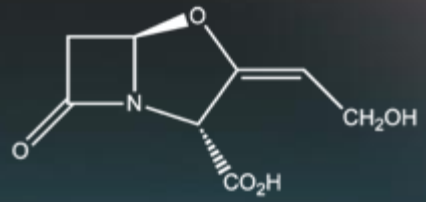


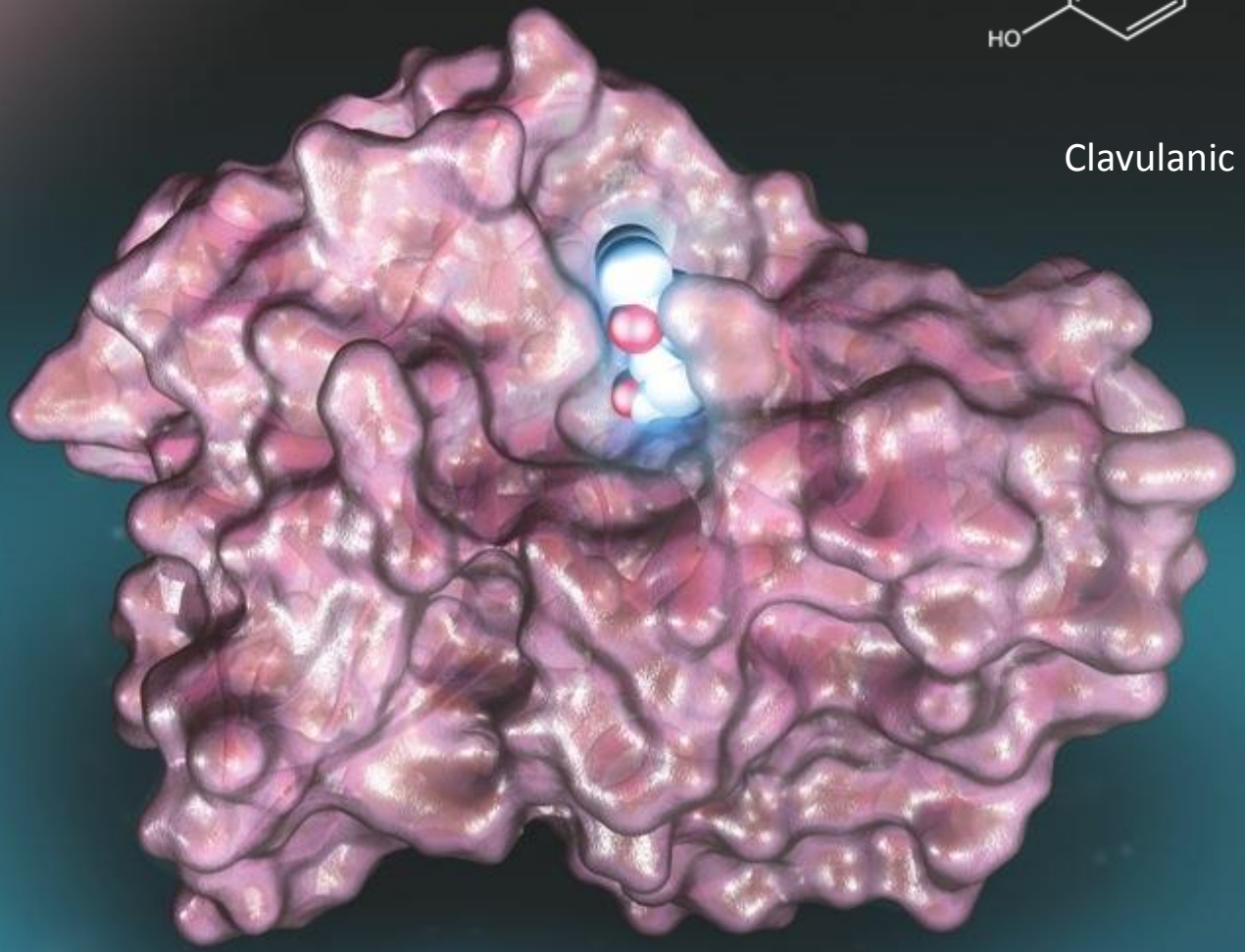
The drug carbidopa (Lodosyn; highlighted in pink) is used together with levodopa (in blue) to manage the symptoms of Parkinson's disease caused by a loss of dopamine-producing neurons. In the blood stream, carbidopa protects levodopa from being prematurely converted to dopamine by the enzyme DOPA decarboxylase[1]. Once levodopa crosses the blood-brain barrier, it is converted to dopamine by DOPA decarboxylase, supplementing the dwindling dopamine levels. The chemical structure of carbidopa ensures that it does not readily cross the blood-brain barrier.

Amoxicillin

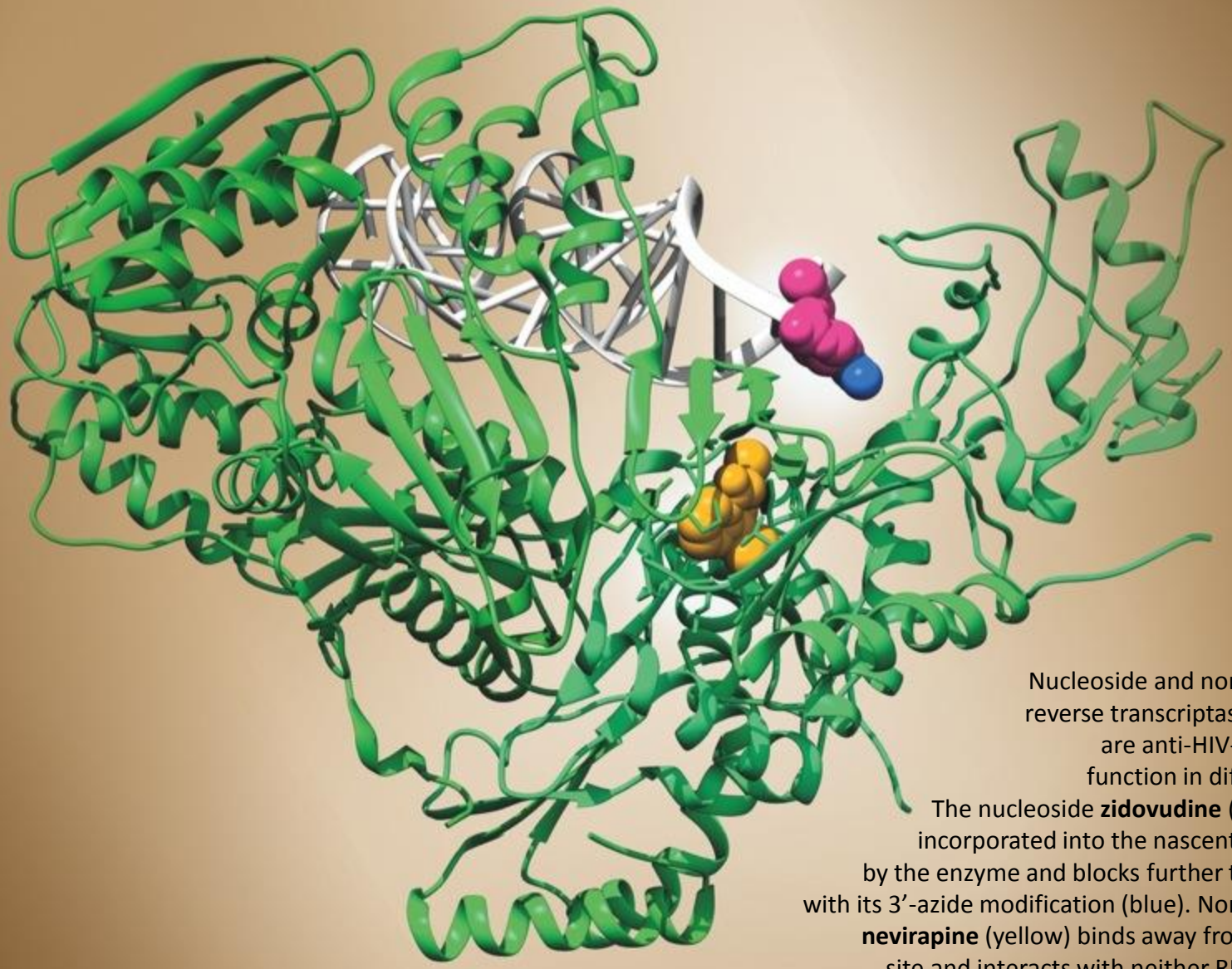


Clavulanic acid

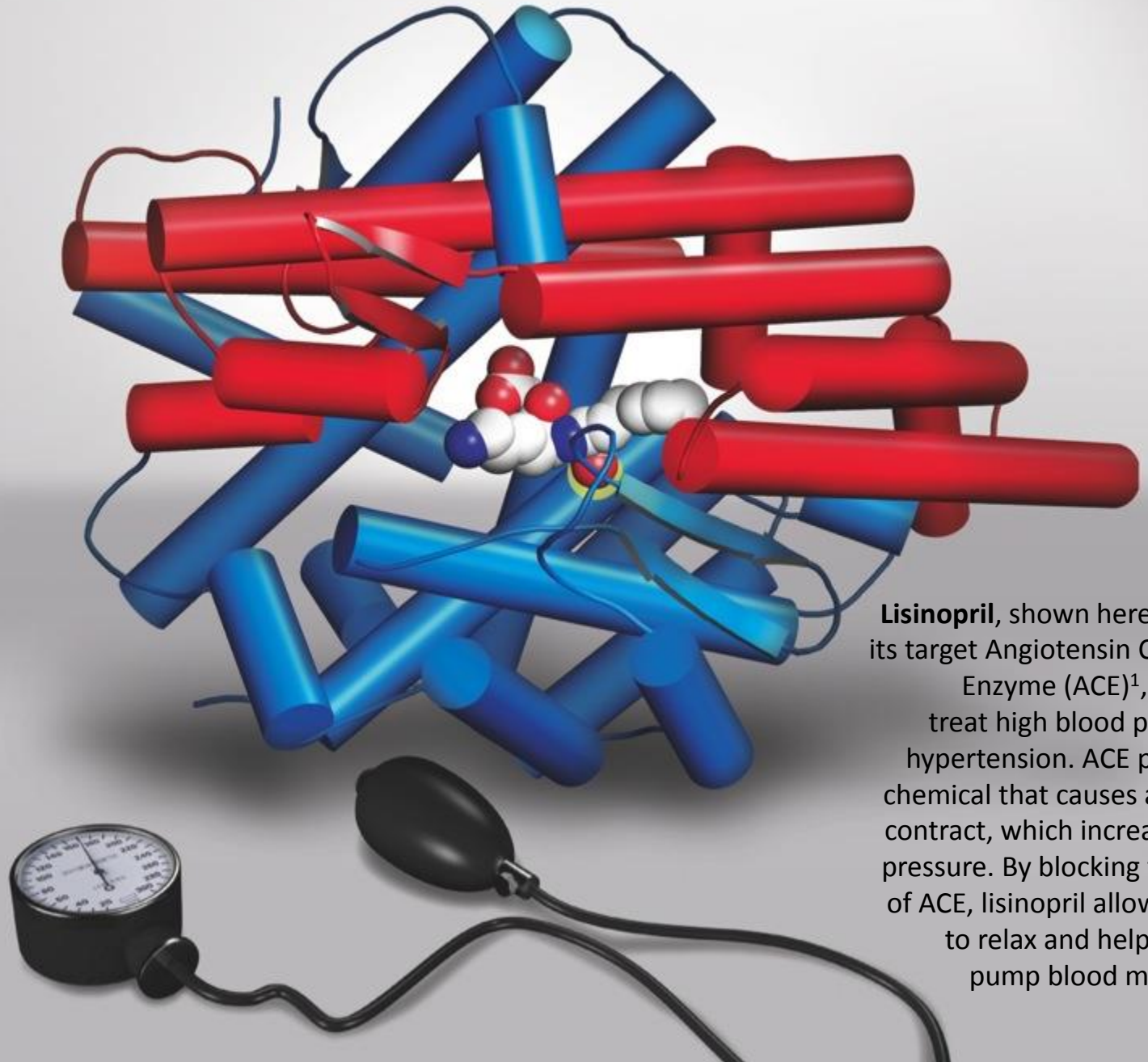




Many drug-resistant bacteria use enzymes called β-lactamases to inactivate penicillin-like antibiotics, including **amoxicillin**. One way to overcome this problem is to prescribe traditional antibiotics in conjunction with another drug that blocks the action of β-lactamase. This structure reveals how one such second agent, **clavulanic acid**, becomes irreversibly bound to the active site of β-lactamase[1], thereby ensuring the efficacy of amoxicillin.

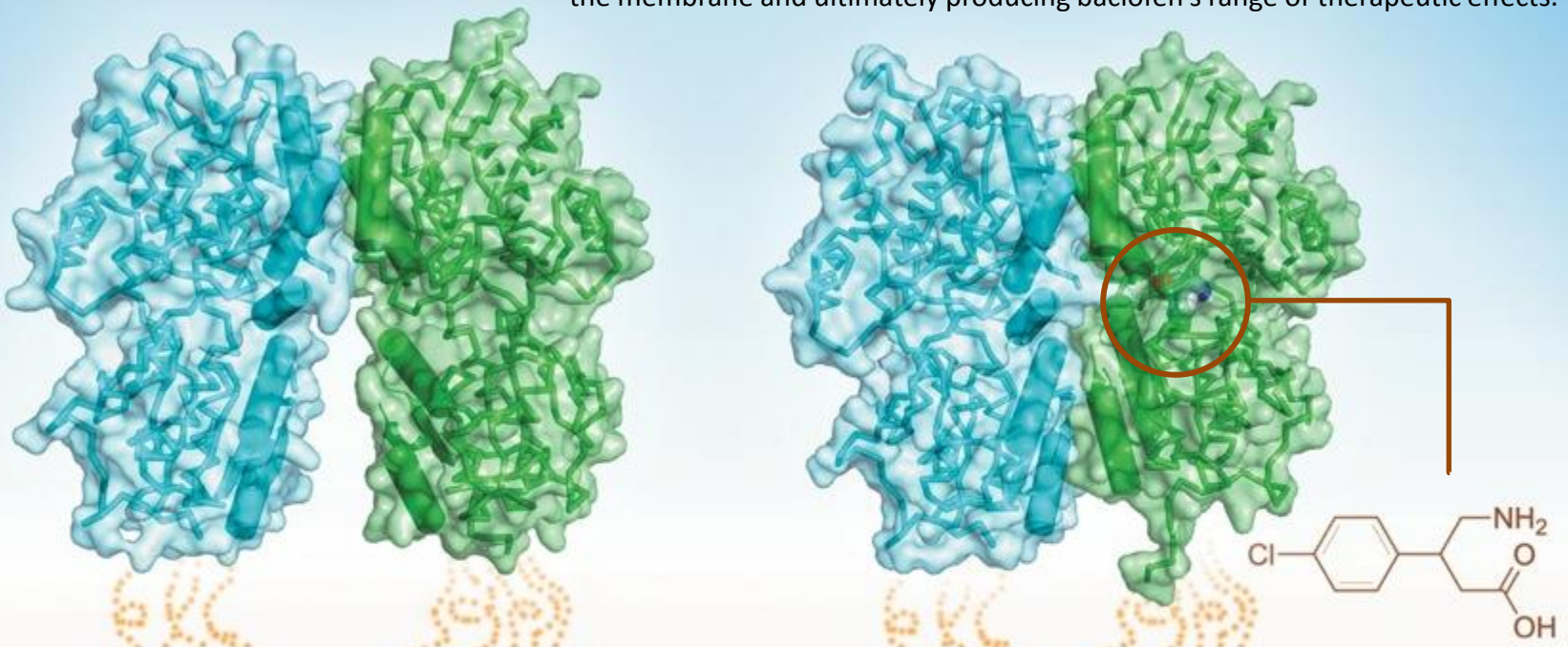


Nucleoside and non-nucleoside reverse transcriptase[1] inhibitors are anti-HIV-1 drugs that function in different ways. The nucleoside **zidovudine** (**AZT**, pink) is incorporated into the nascent DNA strand by the enzyme and blocks further transcription with its 3'-azide modification (blue). Non-nucleoside **nevirapine** (yellow) binds away from the active site and interacts with neither RNA nor DNA. Its mechanism of action is not yet fully understood.



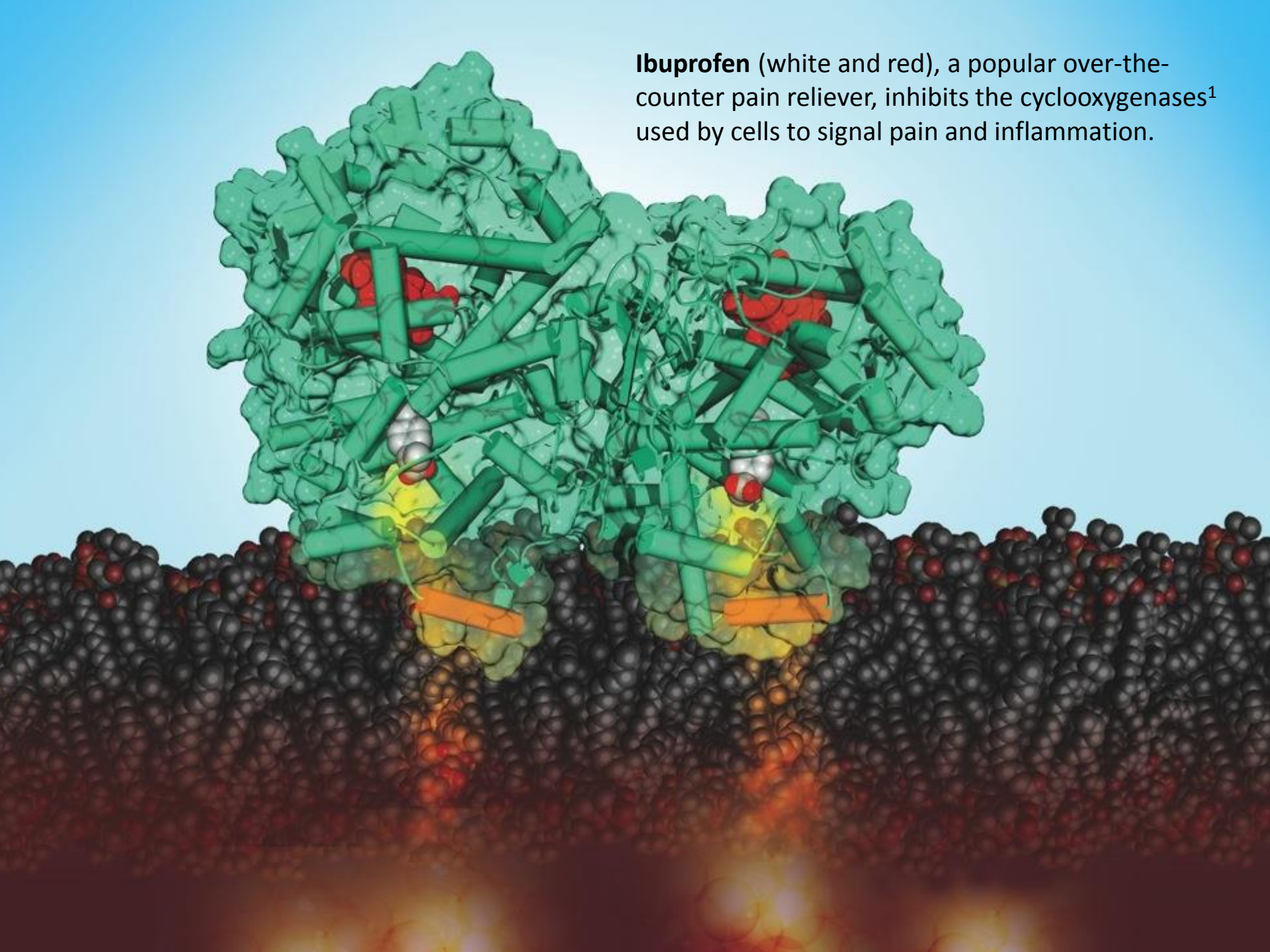
Lisinopril, shown here bound to its target Angiotensin Converting Enzyme (ACE)[1], is used to treat high blood pressure or hypertension. ACE produces a chemical that causes arteries to contract, which increases blood pressure. By blocking the action of ACE, lisinopril allows arteries to relax and help the heart pump blood more easily.

Baclofen is a muscle relaxant and antispastic used to treat patients with multiple sclerosis, cerebral palsy, and spinal cord injuries. Baclofen binding to $GABA_B$[1] induces conformational changes, activating signal transduction pathways across the membrane and ultimately producing baclofen's range of therapeutic effects.

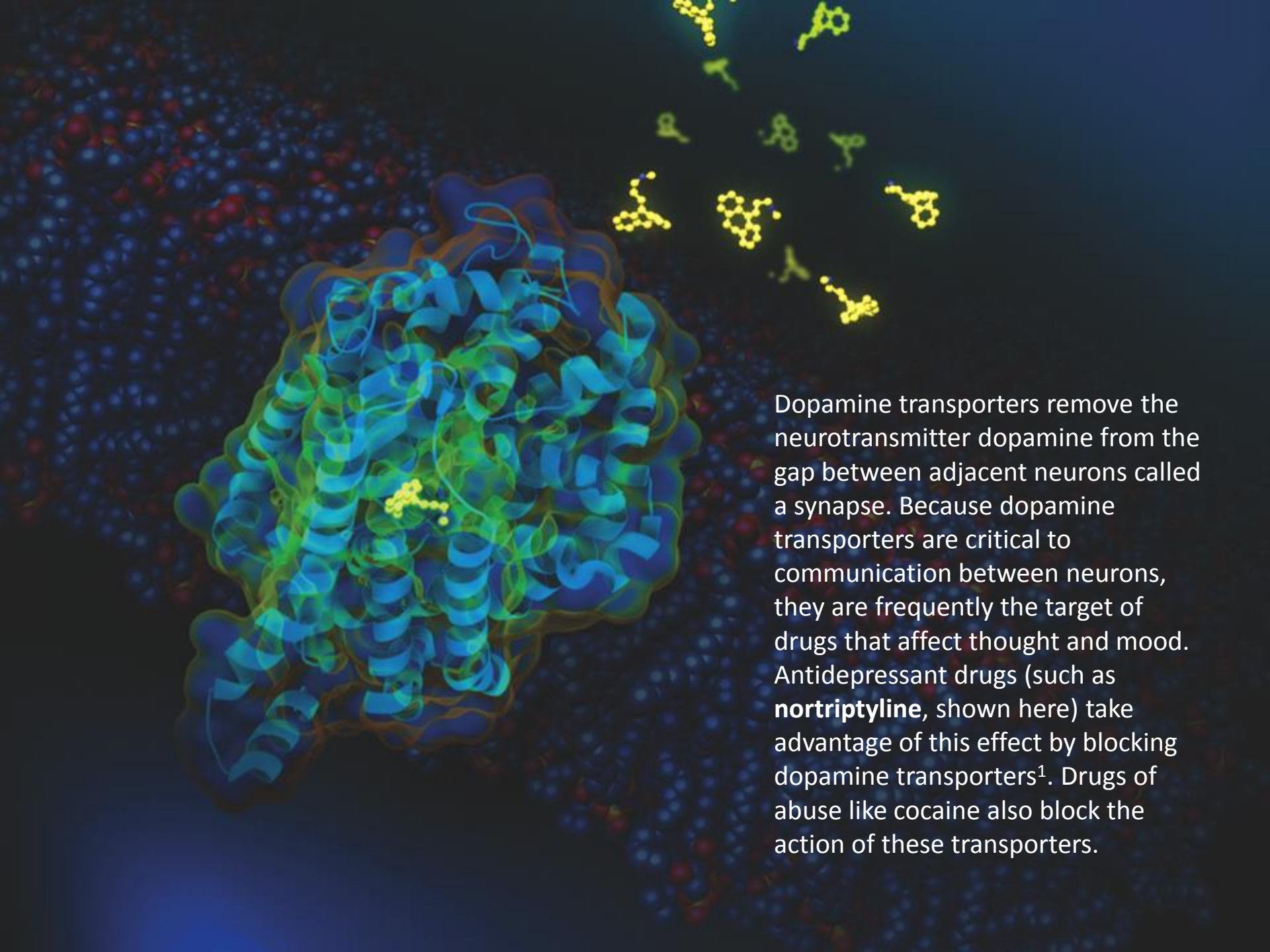


Resting Sate

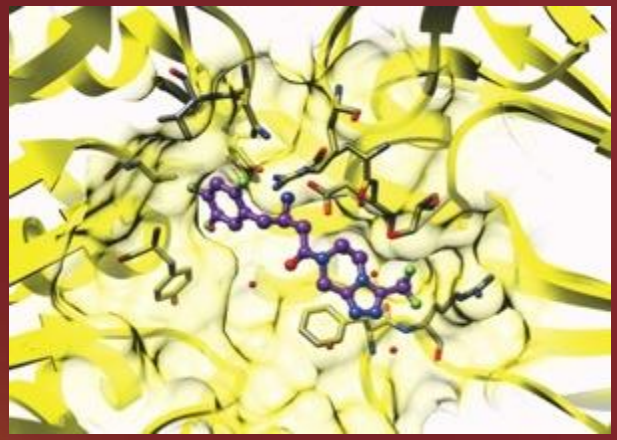
Active State with Baclofen



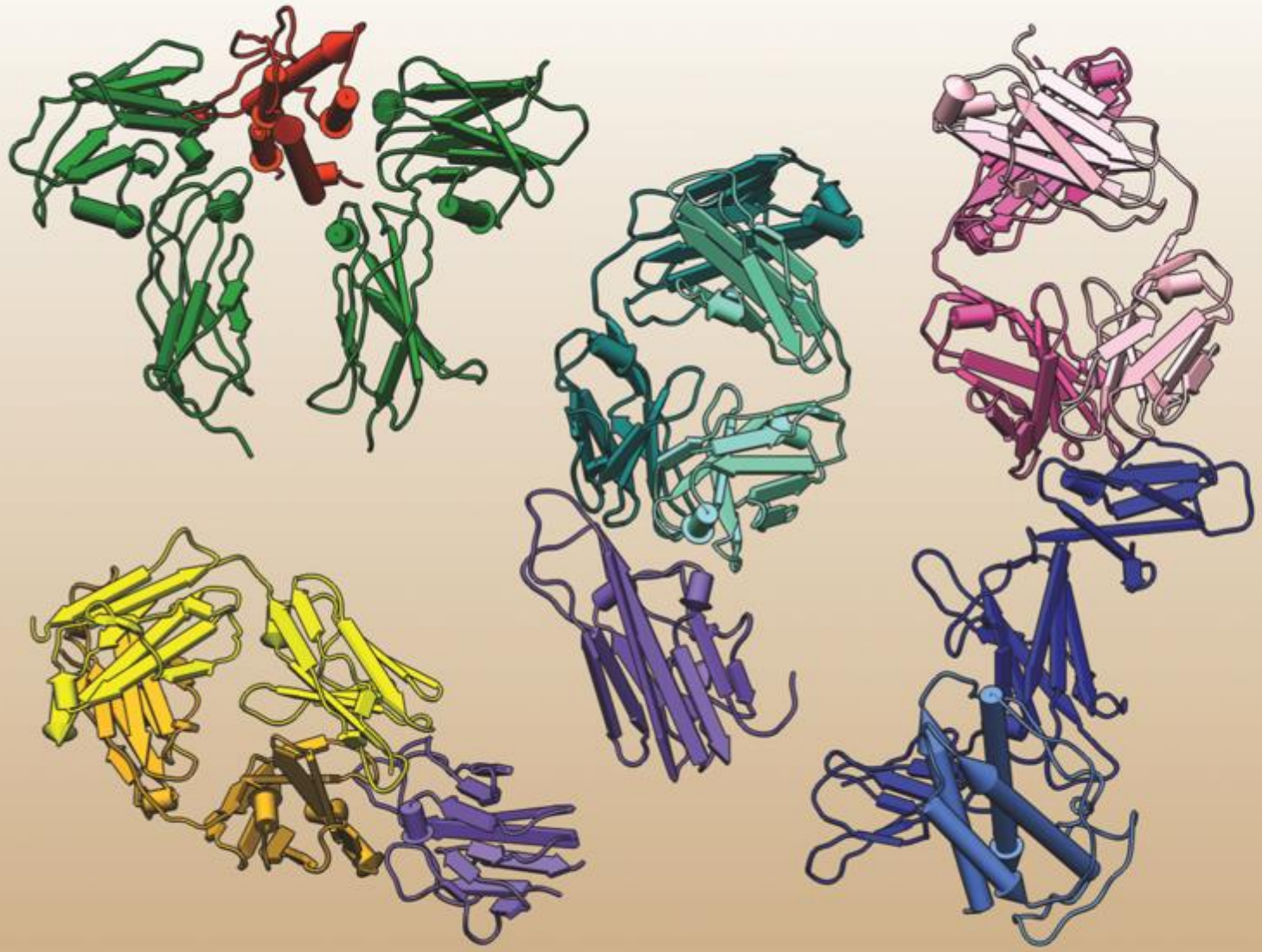
Ibuprofen (white and red), a popular over-the-counter pain reliever, inhibits the cyclooxygenases[1] used by cells to signal pain and inflammation.



Dopamine transporters remove the neurotransmitter dopamine from the gap between adjacent neurons called a synapse. Because dopamine transporters are critical to communication between neurons, they are frequently the target of drugs that affect thought and mood. Antidepressant drugs (such as **nortriptyline**, shown here) take advantage of this effect by blocking dopamine transporters[1]. Drugs of abuse like cocaine also block the action of these transporters.



In Type 2 Diabetes, the enzyme DPP-4[1] is responsible for degrading hormones that stimulate the pancreas to release insulin. **Sitagliptin** (**Januvia**) blocks the action of DPP-4 to keep these hormones in the blood stream longer than normal, thereby stimulating the pancreas to make more insulin. As a result, blood sugar is better controlled, and sugar-induced damage to eyes, kidneys, blood vessels, and nerves can be prevented.



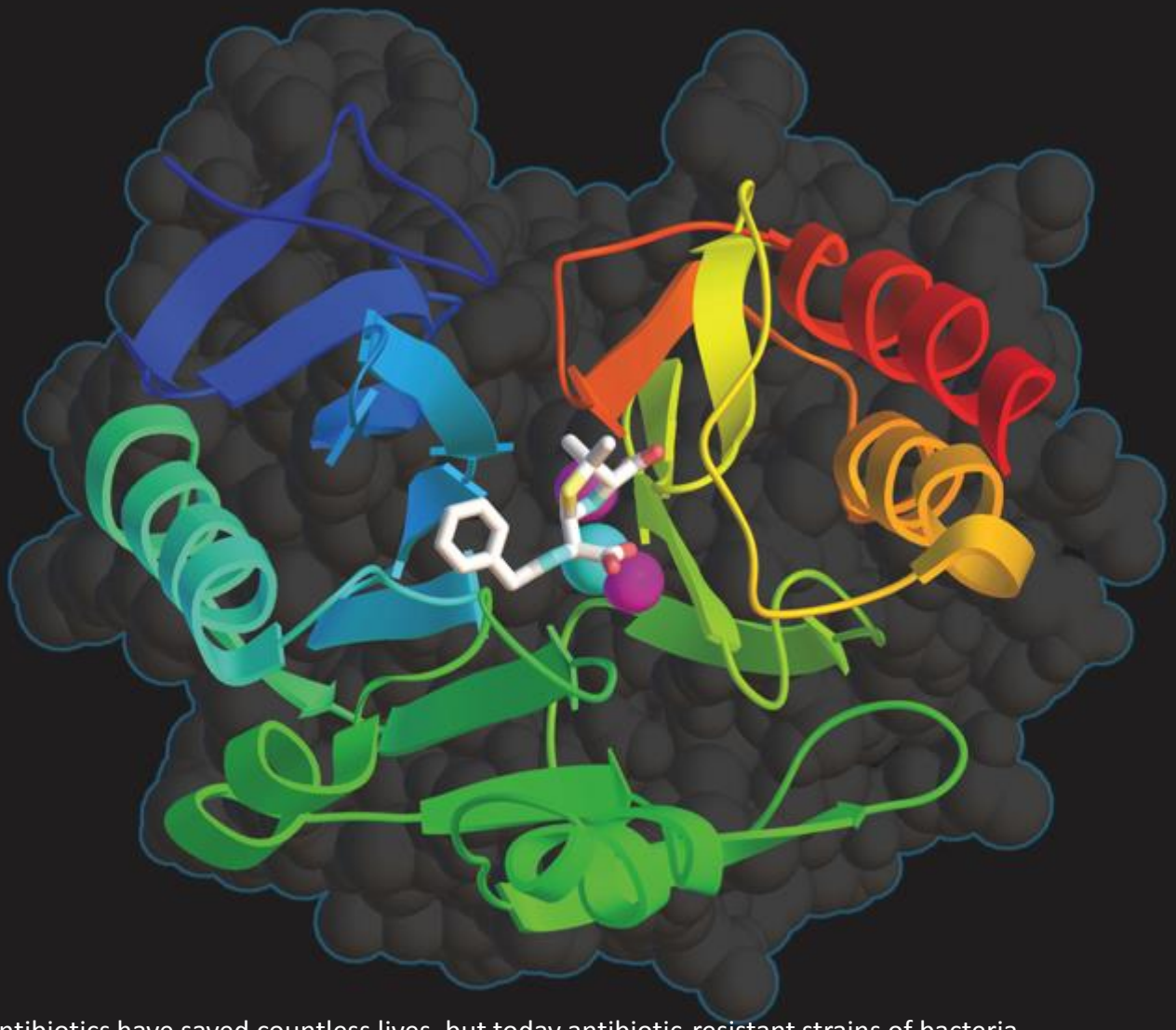
Many proteins are used in the treatment of disease.

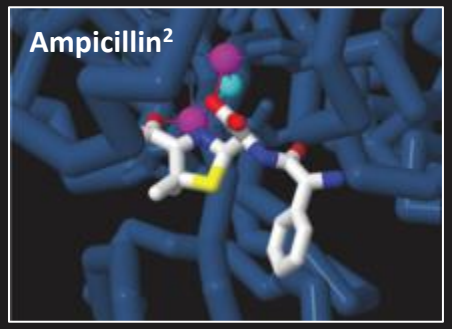
The hormone erythropoietin (red), shown bound to erythropoietin receptor (green)[1], is used to treat anemia.

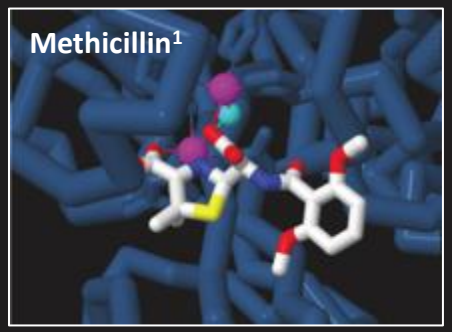
Monoclonal antibodies infliximab (yellow)[2] and adalimumab (aqua)[3] bind to tumor necrosis factor alpha (purple) and are approved for the treatment of arthritis, psoriasis, and Crohn's disease.

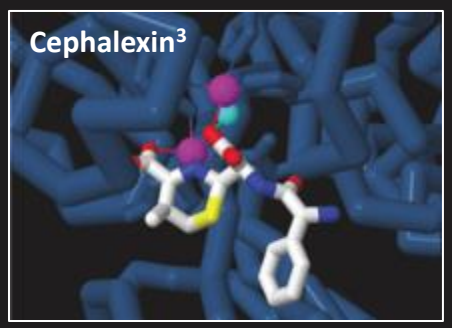
The monoclonal antibody ustekinumab (pink) binds to Interleukin 12 (dark blue)[4] and is a treatment for psoriasis.

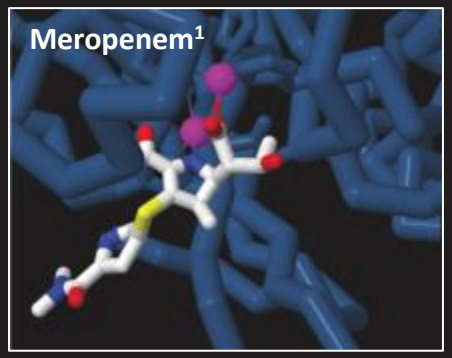
Only the antigen-binding fragments of antibodies are shown here.











Antibiotics have saved countless lives, but today antibiotic-resistant strains of bacteria represent a dangerous new global threat. Bacteria that possess the recently characterized NDM-1 metallo-β-lactamase enzyme[1] are particularly worrisome. NDM-1 is unique in that it can inactivate all approved penicillin-like antibiotics. PDB structures reveal how NDM-1 can adjust its shape to inactivate antibiotics, including our most advanced carbapenem antibiotics.

Protein-Drug Complexes

Proteins are tiny molecular machines. While not visible with the naked eye, their structures and functions can be investigated and understood through various experimental methods. Proteins perform many of the tasks needed to support living cells. Illnesses, such as cancer, can occur when they are prevented from performing their normal jobs. Other ailments are caused when foreign proteins (such as from bacteria or viruses) interfere with ours. Most drugs are small chemicals, even smaller than proteins, that work by binding to target proteins and modifying their actions within our cells. Other drugs are modified proteins that can take the place of improperly operating native proteins.

Some of our most powerful anticancer drugs completely disable an essential molecular machine, without which the cell cannot survive. These drugs kill cancer cells outright. Other drugs, such as cholesterol lowering agents, blunt the action of less-critical proteins to benefit patients.

We know a great deal about how drugs work because scientists in academe and the pharmaceutical industry are able to examine drug-protein complexes at the level of individual atoms. These three-dimensional (3D) atomic structures allow us to see how drugs bind to their protein targets in exquisite detail. Frequently, these structures suggest ways to modify the structure of the drug to better fit the target protein, either to improve efficacy or to reduce the likelihood of side effects.

These structures of proteins and drugs, along with many others, can be explored at the RCSB PDB (rcsb.org).

About the RCSB PDB

RCSB PDB is a vital resource for biological research and education worldwide.

It provides enhanced access to information about the 3D structures of more than 110,000 nucleic acids, proteins, and large molecular machines contained in the Protein Data Bank (PDB) archive.

The RCSB PDB supports the development of standards for the representation, annotation, and validation of these structural data that are collected from different experimental methods. Tools for query, visualization, and analysis of PDB data are developed and made available. An online educational portal is enhanced by online and in-person outreach efforts targeted at promoting a structural view of biology.

RCSB PDB resources are utilized by a variety of researchers, teachers, and students studying biology and its connections to molecular biology, structural biology, computational biology, pharmacology, and more.

RCSB PDB is located at Rutgers, The State University of New Jersey and the University of California, San Diego.

RCSB PDB is supported by a grant (DBI-1338415) from the National Science Foundation, the National Institutes of Health, and the US Department of Energy.

RCSB PDB is a member of the Worldwide Protein Data Bank.

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Acknowledgements

Molecular images were created using UCSF Chimera (E. F. Pettersen, T. D. Goddard, C. C. Huang, et al. (2004) Chimera–a visualization system for exploratory research and analysis. J Comput Chem 25: 1605-1612.), PyMOL (The PyMOL Molecular Graphics System, Version 1.7.4 Schrödinger, LLC.), and PMV (M. F. Sanner (1999) Python: A Programming Language for Software Integration and Development. J. Mol. Graphics Mod. 17: 57-61.)

Thanks to the many people who helped develop this calendar: Luigi Di Costanzo, Sutapa Ghosh, David S. Goodsell, Rachel Kramer Green, Brian Hudson, Yu-He Liang, Ezra Peisach, Irina Persikova, Monica Sekharan, Chenghua Shao, Maria Voigt, Christine Zardecki, and Stephen K. Burley.