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PROTEIN DATA BANK AS A GOLDMINE IN DRUG DISCOVERY

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ABSTRACT

Protein-ligand binding is the notion that a small molecule (a drug, aka. the ligand) binds to a receptor or protein in the body. This binding event evokes a biological response, possibly the reduction of inflammation, pain relief, etc. Typically, there are a limited number of poses or configurations that this protein-ligand complex can assume (or possibly only one). Identifying this bio-active pose is a tremendous challenge in drug discovery. Frequently, it is thought to be the lowest energy pose for either the protein or the ligand, but that is typically not the case. The complex can stabilize or make up for a higher energy conformation of the ligand, etc. Both the protein and ligand are three dimensional and flexible and therefore are constantly changing shape. This is a multi-step problem. Starting with the ligand, one has to identify the bioactive 3D conformation of the ligand. Moving on then to the protein, the bioactive conformation is an even bigger challenge partially because the molecule is so much bigger and there are more possibilities. Lastly, if one could identify both the bioactive conformation of the ligand and the protein, then one is challenged to place the ligand in the correct location and orientation within the protein to produce the desired activity. There are many ways to generate these poses, as well as many ways to try to determine which ones are (or may be) correct. Some of these calculations are computationally inexpensive, while others may be extraordinarily expensive. One approach to this problem is to generate a large number of potential poses using a fairly inexpensive method and follow that up with a more expensive calculation to rank them in order of likelihood of being the bio-active pose. However, it is still easy to generate many more potential poses than one can afford to apply an expensive method.

KEYWORDS: chimera, rule of five, ligand, docking, protein, druggability, spresi.

INTRODUCTION

The Protein Data Bank (PDB) is a database of known crystal structures and Nuclear Magnetic Resonance (NMR) structures, many of which are protein-ligand complexes. By mining the information contained in these structures, it is generating a scoring function based on known protein-ligand interactions. That is why it is the process through the entire PDB to extract out the interactions between small molecules and proteins. The output of the reduce code is the set of observed interactions after applying a distance bin technique. The distance bins simplify the comparison of a potential interaction to the actual observed interactions. This is just taking a set of observed distances and clumping them together. In order to include some of the atomic environment information, atom types are used rather than simply using the atomic element. This differentiates between aromatic and aliphatic carbons, nitrogens that are in an amide bond versus a primary amine, etc. Once the counts of the observations are tallied, one can transform them into percentages of the time that a given interaction is observed. Protein Data Bank and Drug Bank both are simultaneously *vice-versa* to each other.[1]

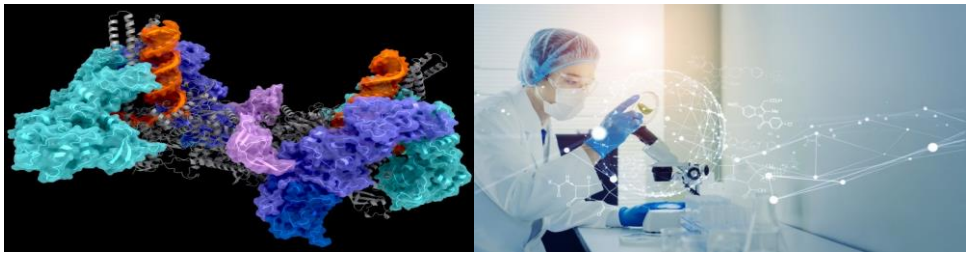

Figure-1: Protein ligand & target.

The Protein Data Bank (PDB) is an archive of experimentally determined three-dimensional structures of proteins, nucleic acids, and other biological macromolecules. Program database (PDB) is a file format (developed by Microsoft) for storing debugging information about a program (or, commonly, program modules such as a DLL or EXE). PDB files commonly have a pdb extension. A PDB file is typically created from source files during compilation. Every experimental structure in the PDB is assigned a 4-character alphanumeric identifier called the PDB identifier or PDB ID (e.g., 2hbs). In some cases, large groups of structures (e.g., a protein bound to a series of different inhibitors/drugs) are submitted to the PDB. The PDB format accordingly provides for description and annotation of protein and nucleic acid structures including atomic coordinates, secondary structure assignments, as well as atomic connectivity. In addition experimental metadata are stored. PDB is a very important database when it comes to the areas of structural biology. Structures in PDB have wide applications. They can be used for various studies including identification of new protein structures via *in-silico* approaches or can be used for protein–nucleic acid interaction studies. The module pdb defines an interactive source code debugger for Python programs. It supports setting (conditional) breakpoints and single stepping at the source line level, inspection of stack frames, source code listing, and evaluation of arbitrary Python code in the context of any stack frame. The Protein Data Bank (PDB) file format is a textual file format describing the three-dimensional structures of molecules held in the Protein Data Bank, now succeeded by the mmCIF format. The PDB format accordingly provides for description and annotation of protein and nucleic acid structures including atomic coordinates, secondary structure assignments, as well as atomic connectivity. In addition experimental metadata are stored. The PDB format is the legacy file format for the Protein Data Bank which has kept data on biological macromolecules in the newer PDBx/mmCIF file format since 2014. The PDB is overseen by an organization called the Worldwide Protein Data Bank. The PDB is a key in areas of structural biology, such as structural genomics. Most major scientific journals and some funding agencies now require scientists to submit their structure data to the PDB. The role of the power distribution box is to distribute the electrical supply to the various circuits. Thanks to it, it is possible to control all the elements belonging to the installation.[2]

Figure-2: Tom Koetzle and Joel L. Sussman; the inventors of PDB.

The Power Distribution Box also contains elements that allow you to quickly and safely cut off the power supply. Enter pdb, Python's built-in interactive source debugger. The acronym 'pdb' stands for Python DeBugger, embodying its core function. The module pdb defines an interactive source code debugger for Python programs. It supports setting (conditional) breakpoints and single stepping at the source line level, inspection of stack frames, source code listing, and evaluation of arbitrary Python code in the context of any stack frame. Conceived as part of Python's standard library, pdb equips developers with an accessible and powerful tool to spot bugs effectively. You can view and edit Protein Data Bank files in Windows, Linux, and macOS with Avogadro. These programs can open the file, too: Jmol, RasMol, QuickPDB, and USCF Chimera. Since these are plain text, you can open one in a text editor as well. Protein Data Bank (PDB) format is a standard for files containing atomic coordinates. Structures deposited in the Protein Data Bank at the Research Collaboratory for Structural Bioinformatics (RCSB) are written in this standardized format. The short description provided here will suffice for most users. The PDB distributes coordinate data, structure factor files and NMR constraint files. In addition it provides documentation and derived data. The coordinate data are distributed in PDB and mmCIF formats. A typical PDB formatted file includes a large "header" section of text that summarizes

the protein, citation information, and the details of the structure solution, followed by the sequence and a long list of the atoms and their coordinates. The PDB was established in 1971 at Brookhaven National Laboratory under the leadership of Walter Hamilton and originally contained 7 structures. After Hamilton's untimely death, **Tom Koetzle** began to lead the PDB in 1973, and then Joel Sussman [**Joel L. Sussman** (born September 24, 1943) is an Israeli crystallographer best known for his studies on acetylcholinesterase, a key protein involved in transmission of nerve signals. He is the Morton and Gladys Pickman Professor of Structural Biology at the Weizmann Institute of Science in Rehovot and its director of the Israel Structural Proteomics Center] in 1994.

Disadvantages of PDB format: The format is not designed for computer extraction of information from the records. The Protein Data Bank (PDB) is an archive of experimentally determined three-dimensional structures of proteins, nucleic acids, and other biological macromolecules. PDB has a 25 year history of service to a global community of researchers, educators, and students in a variety of scientific disciplines. The Protein Data Bank (PDB) archive currently holds > 155,000 atomic-level 3D structures of biomolecules experimentally determined using crystallography, nuclear magnetic resonance spectroscopy, and electron microscopy. The PDB archive contains 5,914 structures containing one of the known targets and/or a new drug, providing structural coverage for 88% of the recently approved NMEs across all therapeutic areas. The three main techniques used are X-ray crystallography, NMR spectroscopy, and 3D electron microscopy. The chart Number of Released PDB Structures per Year illustrates the annual growth in usage of each method per year since the start of the archive. A PDB is a user-created set of schemas, objects, and related structures that appears logically to a client application as a separate database. Every PDB is owned by SYS, regardless of which user created the PDB. The primary use of protein structure for the development of drug compounds is to determine the structure of a protein in complex with a tool compound (a known ligand or lead inhibitor) for the purpose of suggesting a new chemical hypothesis in order to improve inhibitor affinity by suggesting new chemical modifications.

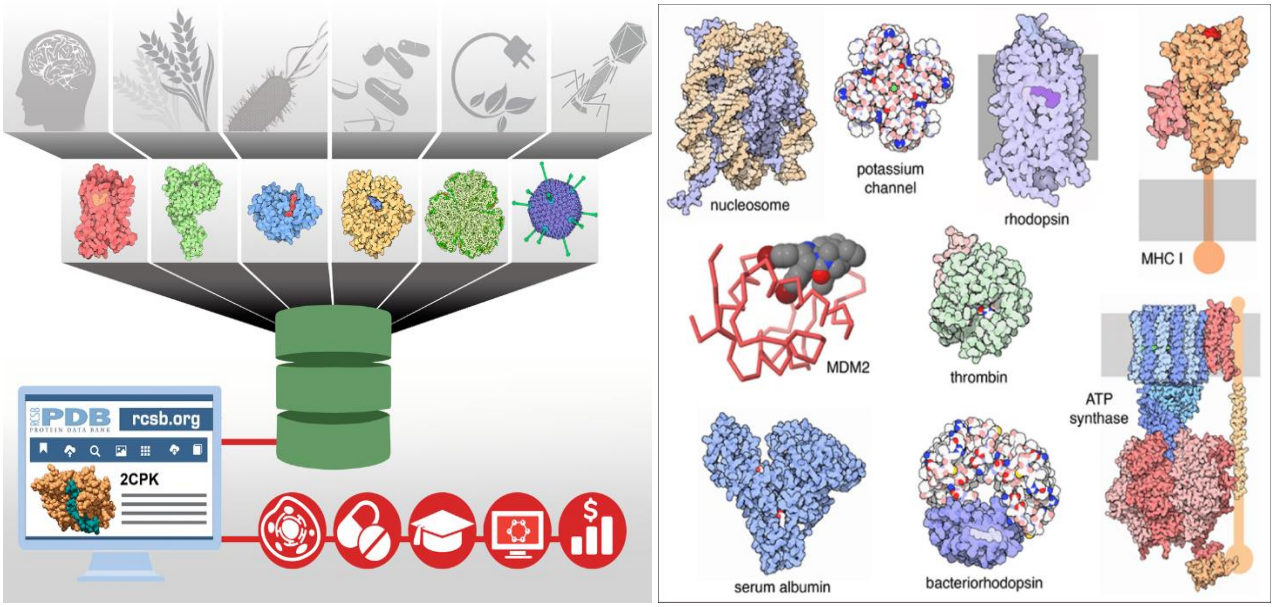

Figure-3: PDB in various format.

The Genesis of PDB: The Protein Data Bank originated from the collaborative efforts of biophysicists and molecular biologists who recognized the need for a centralized repository to store and share three dimensional structures of biological macromolecules. Established in 1971, PDB began as a small collection of protein structures determined by X-ray crystallography.[3]

Over the years, PDB has evolved into a global archive, embracing advancements in technology and expanding its scope to include structures determined by various experimental techniques, such as nuclear magnetic resonance (NMR) spectroscopy and cryo-electron microscopy (cryo-EM).

Key Objectives of PDB: Data Archiving: PDB serves as a secure repository for the deposition and storage of experimentally determined structures of biological macromolecules, including proteins, nucleic acids, and large complexes. This data includes atomic coordinates, experimental details, and associated metadata.

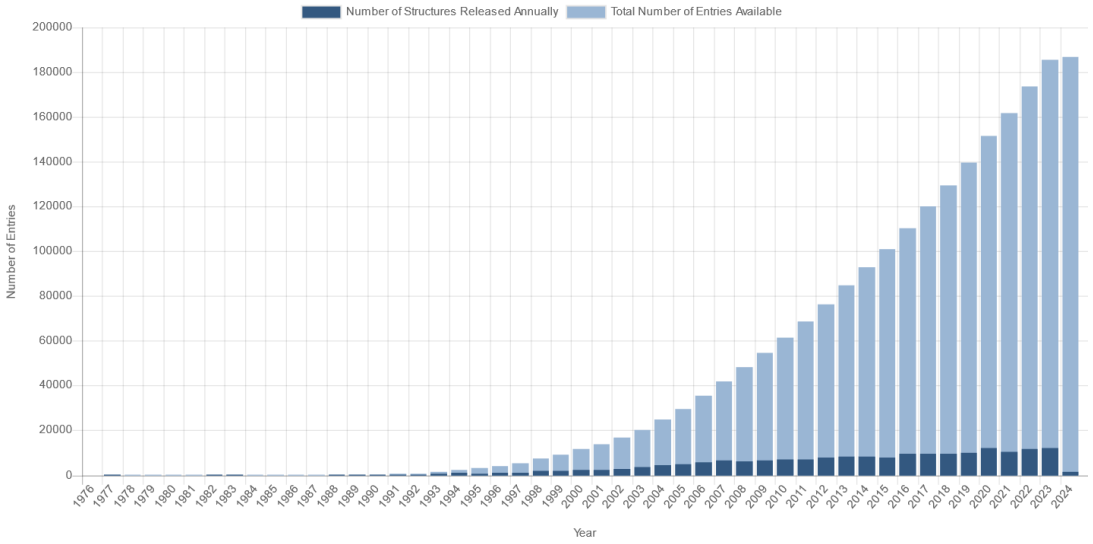

Figure-4: Histogram of structures vs year.

Global Collaboration: PDB is a testament to the power of collaboration in science. It operates as a global effort with data contributed by researchers and institutions worldwide. This collaborative model fosters the exchange of knowledge, accelerates research, and promotes transparency in the scientific community.

Open Access: PDB follows an open-access model, ensuring that the wealth of structural information it houses is freely accessible to scientists, educators, students, and the general public. This openness encourages innovation and serves as a catalyst for breakthroughs in various scientific disciplines.

Structural Biology Advancements: By providing a centralized repository of high-quality structural data, PDB has played a pivotal role in advancing the field of structural biology. Researchers can access a diverse array of structures, gaining insights into the fundamental principles governing biological molecules.

Drug Discovery and Design: PDB is a goldmine for drug discovery and design. Understanding the three-dimensional structures of target proteins allows scientists to design drugs that specifically interact with these molecules, optimizing therapeutic efficacy while minimizing side effects.

Education and Outreach: PDB is not only a resource for seasoned researchers but also a valuable educational tool. It supports educational initiatives by providing a platform for students to explore and understand molecular structures, fostering a deeper appreciation for the complexities of life.

Evolution and Technological Advancements: PDB has continuously evolved to keep pace with technological advancements in structural biology. The integration of structures determined by [Cryogenic electron microscopy] cryo-EM, a revolutionary technique for imaging large biological complexes, has expanded the scope of PDB to include macromolecular assemblies and cellular structures at unprecedented resolutions. Moreover, the development of tools and resources like the Protein Workshop and the RCSB PDB website has made it easier for researchers to visualize and analyze protein structures, facilitating a more comprehensive understanding of their functions.

PDB has now been replaced by **3DB (Three-Dimensional Biomolecular Structures Database),** which will continue to operate at Brookhaven National Laboratory.

The challenge of the new 3DB is to keep pace with ever-increasing data, store data as error-free as possible, and organize and present that data in a way that facilitates information retrieval, knowledge discovery, and non-invasive evaluation. Available services. Over the last two years, PDB has evolved significantly in terms of data management and archive access, evolving into a more powerful tool that combines the results of oriented and relational database systems. 3DB will transform PDB from a disposable database into a comprehensive knowledge base for storing and accessing structured data. This process will increase, prevent users from making major changes and ensure a high degree of compatibility with existing software and compatible users such as browsers.

Utility of PDB structures for small-molecule drug discovery and development: Over the past two decades, structural biologists and structure-guided drug discovery have become firmly established within the biopharmaceutical industry. 3D structures can explain how small-molecule ligands bind to their target proteins. Structural Data have also been shown to help overcome some of the challenges in converting biochemically active compounds into potent drug molecules suitable for safety and efficacy in animals and humans. Many, perhaps all, of the world's major biopharmaceutical companies store copies of PDB data in firewalls.

Bringing PDB files inside the firewall allows interaction between publicly available PDB standards and standards developed by each company. A conservative estimate suggests that, compared to the size of the current PDB, all protein structures are kept as trade secrets within corporate firewalls. The willingness of business biologists (and corporate leaders) to contribute some of this knowledge to the PDB is not only useful but also critical to supporting continued technological innovation in experimental and computational ecosystems. Public-domain 3D structure data archived in the PDB are used in small-molecule drug discovery and early-stage drug development at five points within the process.

Target biology: Function follows form in biology. Atomic-level 3D structures made freely available from the PDB provide functional insights that are not always readily apparent from amino acid sequence. Simply put, there is no substitute for a direct look at the 3D structure of a potential drug discovery target. This information helps researchers understand how it works at the atomic level (i.e., molecular mechanism) and how it contributes to human health and disease. Equally important, use of 3D structures to interpret the results of human genome sequencing studies (e.g., driver mutations specific to tumors, genome-wide associations) influences target selection in many therapeutic areas. Industry colleagues have frequently remarked to me that "the first thing they do when starting a new drug-discovery project is to search the PDB and look hard at potential target structure(s)." Developing the fullest possible understanding of the role that a given drug discovery target plays in human health and disease represents a critical determinant of success. An influential industry-wide analysis of the causes of attrition during drug discovery and development campaigns documented that efficacy failures account for an overall attrition rate of nearly 30%. A more recent analysis identified lack of efficacy as the cause of up to 66% of failures during Phase II clinical trials. Efficacy failures occur when the drug candidate engages the target, achieves the desired biochemical end point (e.g., enzyme inhibition) without serious adverse events, yet fails to deliver the desired clinical benefit. Hence, the importance of gaining comprehensive knowledge of target biology well before embarking on expensive and lengthy human clinical trials.[4]

Target druggability: 3D structures enable visualization of surface features (e.g., clefts, invaginations) likely to bind small organic compounds and thereby inhibit enzyme action or some other biochemical or biological function. Most of the free energy of small molecules bound to proteins is not from the enthalpic contribution (ΔH), but from the entropic contribution of the Gibbs free energy change (-TΔS) (ΔG = ΔH - TΔS) of the System after ligand binding. Higher resolution MX and 3DEM models of proteins often show low-entropy water molecules with concave features. Target "druggability" is defined as the ability of a target to be therapeutically modulated by medicines, and by definition, the "druggable genome" is comprised of genes that encode proteins that can be modulated by drugs for therapeutic purposes.

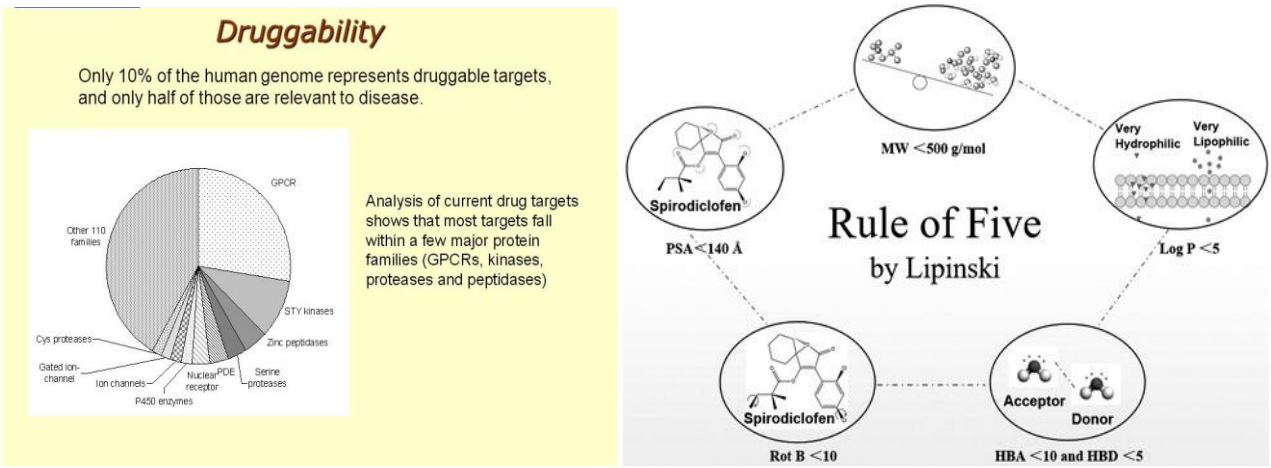

Figure-5: Druggability.

Druggability is a term used in drug discovery to describe a biological target (such as a protein) that is known to or is predicted to bind with high affinity to a drug. Furthermore, by definition, the binding of the drug to a druggable target must alter the function of the target with a therapeutic benefit to the patient. The concept of druggability is most often restricted to small molecules (low molecular weight organic substances) but also has been extended to include biologic medical products such as therapeutic monoclonal antibodies. Drug discovery comprises a number of stages that lead from a biological hypothesis to an approved drug. Target identification is typically the starting point of the modern drug discovery process. Candidate targets may be selected based on a variety of experimental criteria. These criteria may include disease linkage (mutations in the protein are known to cause a disease), mechanistic rationale (for example, the protein is part of a regulatory pathway that

is involved in the disease process), or genetic screens in model organisms. Disease relevance alone however is insufficient for a protein to become a drug target. In addition, the target must be druggable. If a drug has already been identified for a target, that target is by definition druggable. If no known drugs bind to a target, then druggability is implied or predicted using different methods that rely on evolutionary relationships, 3D-structural properties or other descriptors.

Precedence-based: A protein is predicted to be "druggable" if it is a member of a protein family for which other members of the family are known to be targeted by drugs (i.e., "guilt" by association). While this is a useful approximation of druggability, this definition has limitations for two main reasons: (1) it highlights only historically successful proteins, ignoring the possibility of a perfectly druggable, but yet undrugged protein family; and (2) assumes that all protein family members are equally druggable.[5]

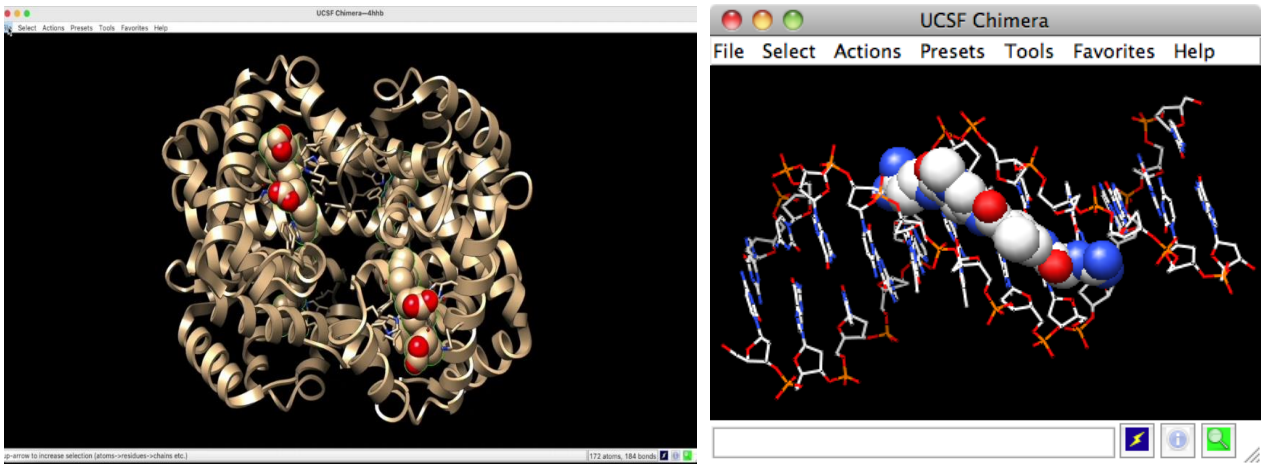

Figure-6: Chimera.

Structure-based: This relies on the availability of experimentally determined 3D structures or high quality homology models. A number of methods exist for this assessment of druggability but all of them consist of three main components.
Identifying cavities or pockets on the structure.
Calculating physicochemical and geometric properties of the pocket.

Assessing how these properties fit a training set of known druggable targets, typically using machine learning algorithms.

Early work on introducing some of the parameters of structure-based druggability came from Abagyan and coworkers and then Fesik and coworkers, the latter by assessing the correlation of certain physicochemical parameters with hits from an NMR-based fragment screen. There are several commercial tools and databases for structure-based druggability assessment. A publicly available database of pre-calculated druggability assessments for all structural domains within the Protein Data Bank (PDB) is provided through the ChEMBL's DrugEBIlity portal. Structure-based druggability is usually used to identify suitable binding pocket for a small molecule; however, some studies have assessed 3D structures for the availability of grooves suitable for binding helical mimetics. This is an increasingly popular approach in addressing the druggability of protein-protein interactions.

Predictions based on other properties: As well as using 3D structure and family precedence, it is possible to estimate druggability using other properties of a protein such as features derived from the amino-acid sequence (feature-based druggability) which is applicable to assessing small-molecule based druggability or biotherapeutic-based druggability or the properties of ligands or compounds known to bind the protein (Ligand-based druggability).

The importance of training sets: All methods for assessing druggability are highly dependent on the training sets used to develop them. This highlights an important caveat in all the methods discussed above: which is that they have learned from the successes so far. The training sets are typically either databases of curated drug targets; screened targets databases (ChEMBL, BindingDB, PubChem etc.); or on manually compiled sets of 3D structure known by the developers to be druggable. As training sets improve and expand, the boundaries of druggability may also be expanded.

Undruggable targets: About 3% of human proteins are known to be "mode of action" drug targets, i.e., proteins through which approved drugs act. Another 7% of the human proteins interact with small molecule chemicals. Based on DrugCentral, 1795 human proteins annotated to interact with 2455 approved drugs. Furthermore, it is estimated that only 10-15% of human proteins are disease modifying while only 10-15% are druggable (there is no correlation between the two), meaning that only between 1-2.25% of disease modifying proteins are

likely to be druggable. Hence it appears that the number of new undiscovered drug targets is very limited. A potentially much larger percentage of proteins could be made druggable if protein–protein interactions could be disrupted by small molecules. However the majority of these interactions occur between relatively flat surfaces of the interacting protein partners and it is very difficult for small molecules to bind with high affinity to these surfaces. Hence these types of binding sites on proteins are generally thought to be undruggable but there has been some progress (by 2009) targeting these sites. Chemoproteomics techniques have recently expanded the scope of what is deemed a druggable target through the identification of covalently modifiable sites across the proteome. When small molecule ligands bind to such clefts, they remove most but not all bound water molecules, moving them to heavy weights and increasing the entropy of the system. Therefore, it is generally believed that finding targeted small molecules that target flatter, relatively featureless protein surfaces (e.g., protein–protein interaction interfaces) versus deeply invaginated clefts characteristic of enzyme active sites. Prequalifying a protein as a target amenable to a small-molecule drug(s) using 3D structure information can increase the probability of finding suitable lead compounds and thereafter reduce the likelihood of attrition during medicinal chemistry optimization.[6]

Small Molecule binding: Public-domain cocrystal structures frequently provide useful precompetitive information concerning binding of tool compounds to potential drug discovery targets. Even more powerful are the many cocrystal structure studies carried out within biopharmaceutical companies that directly assess in 3D how small-molecule hits coming from biochemical or cellbased assays or biophysical measurements bind to would-be drug targets. *In-silico* virtual screening exercises carried out computationally with millions of small molecules can also provide useful information regarding potential starting points for medicinal chemistry.[7]

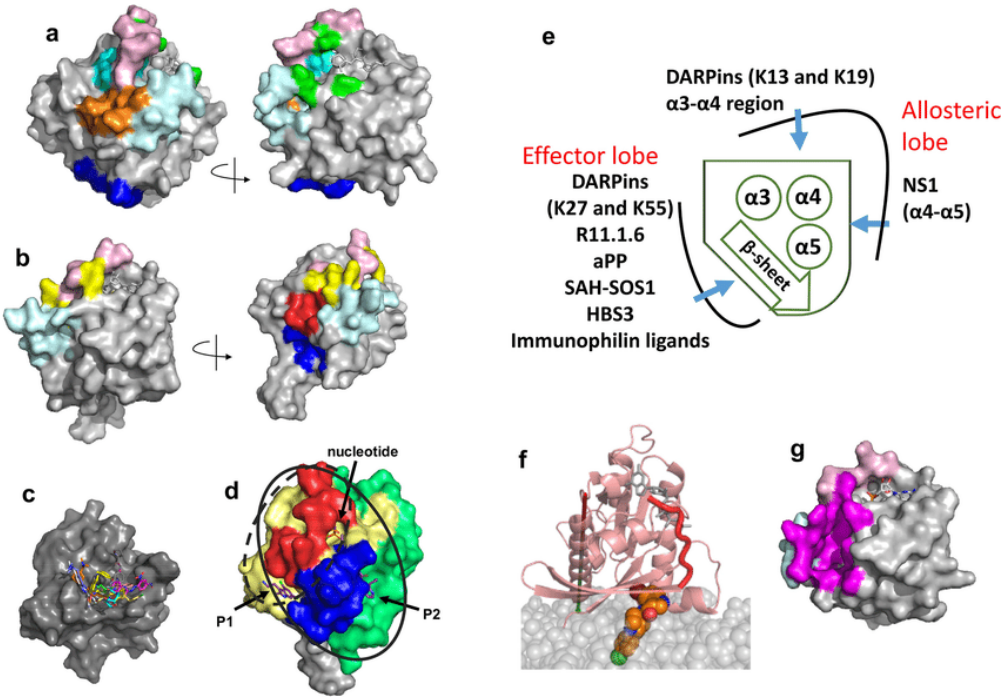

Figure-7: Protein in docking.

Typical fragment or scaffold libraries consist of 500 to 5000 compounds, each with multiple reactive sites capable of supporting automated or semiautomated chemistry with large numbers (i.e., sometimes tens of thousands) of commercially available modifying substituents. Well-designed fragment libraries have the potential to be elaborated into 1015 or more unique chemical structure variations (assuming 1000 fragments each with three sites of chemical diversity with 10,000 possible substituents at each reactive site). Thus, the potential chemical diversity of fragment-based approaches to drug discovery far outstrips even the largest compound screening libraries assembled in either academe or industry (typically no more than a few million compounds).

Notwithstanding this impressive diversity metric, even the best designed fragment library will never provide access to the enormous number of compounds possible. For reference, the number of distinct molecular structures of MW <500 Da containing only carbon, oxygen, nitrogen, hydrogen, and fluorine atoms that obey the valence rules of chemistry is estimated to be 1060. Finally, structural characterization of compound hits detected by any screening method provides valuable insights into how various chemotypes bind (or are predicted to bind) to target proteins. 3D structural

information regarding screening hits that are not selected as fragments/scaffolds for medicinal chemistry optimization is frequently used to support decisionmaking by medicinal chemists. Knowledge of the chemotype binding properties of the target site can motivate selection of chemical substituents with which to modify fragment/scaffold hits. This information can also be used later in the optimization process to further optimize the fit of the elaborated lead compound to its binding site.[8]

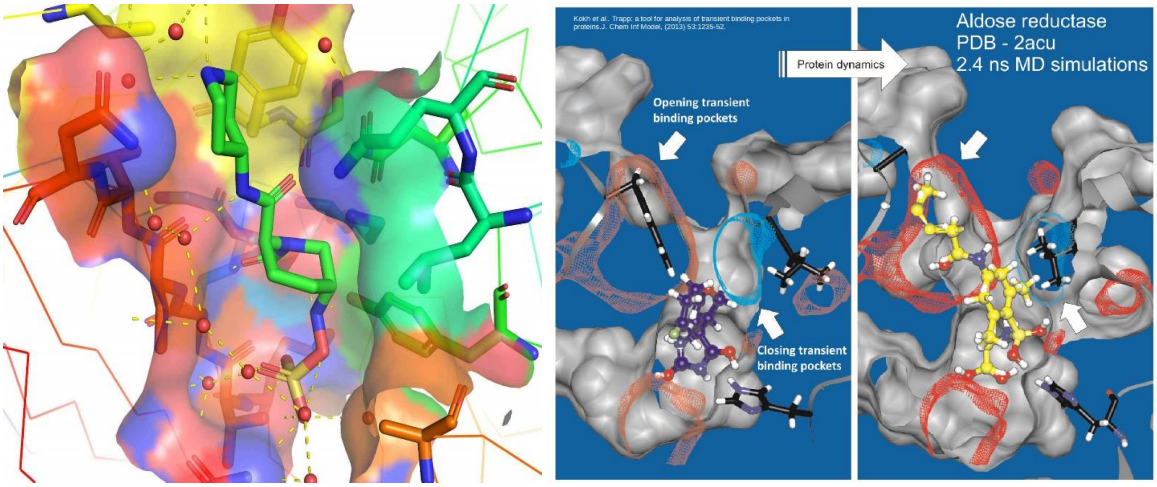

Figure-8: Structure based drug design.

Structure-guided lead optimization: PDB structures and ancillary data stored in the archive regarding sample production, crystallization, etc., constitute important precompetitive information routinely used by drug hunters. Open access to these data (without limitations on usage) facilitates early-stage drug discovery writ large. Whenever practicable, nearly every the major biopharmaceutical company makes intensive use of cocrystal structures to guide optimization of small-molecule ligand potency from screening hits to lead compounds to drug candidates. In the most favorable cases, knowledge of cocrystal structures of potential off-target proteins (e.g., GSK-3β: inhibition of this protein kinase causes hyperglycemia) can be utilized to help ensure the desired selectivity profile and reduce the likelihood of off-target toxicity. In the absence of experimental cocrystal structures of the target protein, in silico docking tools are commonly used to guide lead optimization.[9]

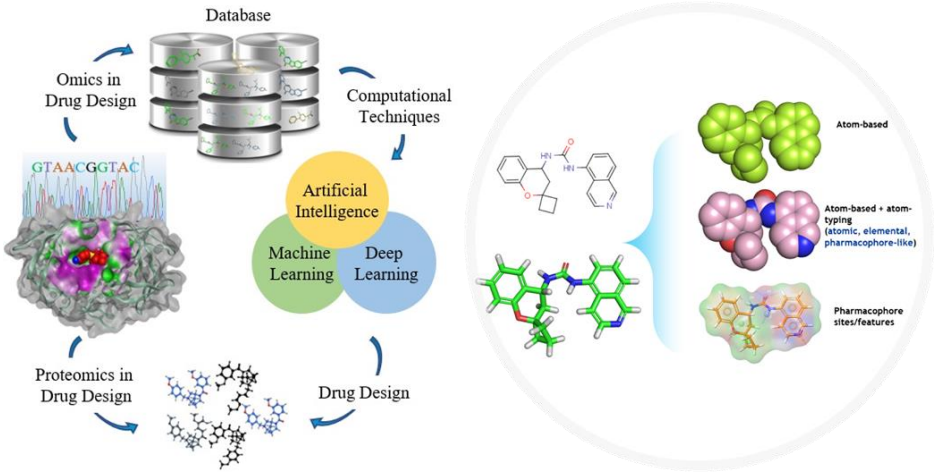

Figure-9: Protein based drug design.

Where an experimental 3D structure of the target protein is not available, homology models are routinely combined with these same in silico docking tools. Machine learning approaches are also being used with increasing frequency to drive medicinal chemistry campaigns. Structural guidance of medicinal chemistry decision-making is particularly important when optimizing the physicochemical properties of would-be drug candidates. Lipinski's "Rule of 5" has often been touted as a basis for determining whether or not a small molecule is "drug like." Close reading of Lipinski's landmark paper, however, reveals that the Rule of 5 pertains to oral bioavailability, not drug likeness per se. Clinical trial experiences have repeatedly shown that more stringent limits on molecular weight (MW < 400 Da instead of 500 Da) are correlated with increased

likelihood of successful outcomes. Lower drug candidate lipophilicity (as judged by cLogP, the calculated log10 of the partition coefficient between octanol and water) is also correlated with improved clinical trial outcomes. Lipophilicity appears to be a critical determinant of nonspecific binding to proteins unrelated to the drug target and consequently unwanted side effects and clinical adverse events. Precise knowledge of how lead compounds bind to target proteins informs decision-making regarding the chemical modifications necessary to maintain cLogP <3 (not <5 as specified in the Rule of 5), while avoiding addition of atoms that increase MW beyond 400 Da. Other molecular design considerations influenced by knowledge of 3D structure focus on avoiding synthesis of overly flat compounds, because small molecules lacking sp^3 carbons and chiral centers tend can be poorly soluble in aqueous solution.[10]

CONCLUSION

PDB is a very important database when it comes to the areas of structural biology. Structures in PDB have wide applications. They can be used for various studi es including identification of new protein structures via in silico approaches or can be used for protein–nucleic acid interaction studies. The primary use of protein structure for the development of drug compounds is to determine the structure of a protein in complex with a tool compound (a known ligand or lead inhibitor) for the purpose of suggesting a new chemical hypothesis in order to improve inhibitor affinity by suggesting new chemical modifications. PDB structures and ancillary data stored in the archive regarding sample production, crystallization, etc., constitute important precompetitive information routinely used by drug hunters. Open access to these data (without limitations on usage) facilitates early-stage drug discovery writ large. A typical PDB formatted file includes a large "header" section of text that summarizes the protein, citation information, and the details of the structure solution, followed by the sequence and a long list of the atoms and their coordinates. Disadvantages of PDB format is not designed for computer extraction of information from the records. The benefits of the Oracle Multitenant architecture include: Access isolation between individual Pluggable Databases (PDBs) stored in the same Container Database (CDB), Ability to manage many databases with the simplicity of managing just one CDB that contains many PDBs. The three main techniques used are X-ray crystallography, NMR spectroscopy, and 3D electron microscopy. The chart Number of Released PDB Structures per Year illustrates the annual growth in usage of each method per year since the start of the archive.

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