Enabling the discovery of degrader molecules to treat the untreatable

Structural information is indispensable for the discovery of degrader drugs in which multiple elements need to yield a functional complex between the proteins and the small molecule.

INTRODUCTION

Captor Therapeutics is a biopharmaceutical company that focuses on developing protein degradation drugs for cancer and autoimmune diseases that have limited or no known treatment options.
Targeted Protein Degradation (TPD) combats the therapeutic limits of small molecules by overcoming drug resistance and uncoupling their pharmacokinetics from pharmacodynamics. Breakthrough TPD technology permits the degradation of virtually any intracellular protein, including the so-called "undruggable proteome". An example of a protein degradation pathway is shown in Figure 1.
Captor Therapeutics takes a multi-faceted approach to eliminating disease-causing proteins. Its proprietary Optigrade™ platform enables the robust discovery of therapeutic compounds with good biopharmaceutical properties.

CHALLENGE

To maximize the probability of developing a successful degrader drug, Captor exploits different approaches to protein degradation: molecular glues, bifunctional degraders, and Obterons®. To unlock the potential of the ubiquitin proteasome system, Captor Therapeutics is developing a large platform of ubiquitin ligases and associated ligands. This approach will allow them to adapt the degradation process to the specific therapeutic indication. Together, these components form the Captors Optigrade™ platform – a robust drug discovery engine.
Today, biologics and small molecule inhibitors represent the main therapeutic modalities applied in cancer and autoimmunity diseases. The totally different mode of action of Captor's TPD drugs allows them to overcome the limits of existing medicines, i.e. there is no need for an active site, thus opening up their application to different protein classes. Consequently, it becomes possible to develop novel therapies against drug targets that have not previously been addressed with classical drugs.
One method to of obtaining a specific and effective drug is structure-based drug design. Iin this approach, the key is to obtain many high-quality target protein structures with successive iterations of the ligand. To achieve this, it is necessary to work closely with a bright synchrotron source.

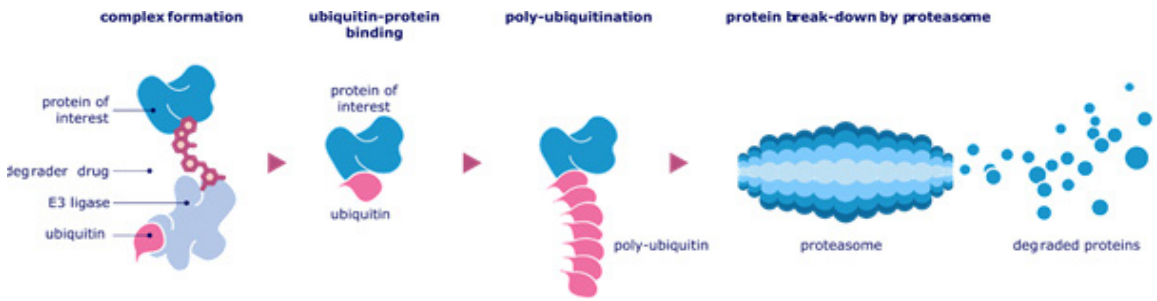

Figure 1: In order to induce the targeted degradation of a disease-related protein, a ternary complex needs to be formed between the protein, an E3 ubiquitin ligase, and a degrader drug. Next, the polyubiquitination of the protein of interest results in the protein's breakdown by a proteasome. (Provided by Captor Therapeutics)

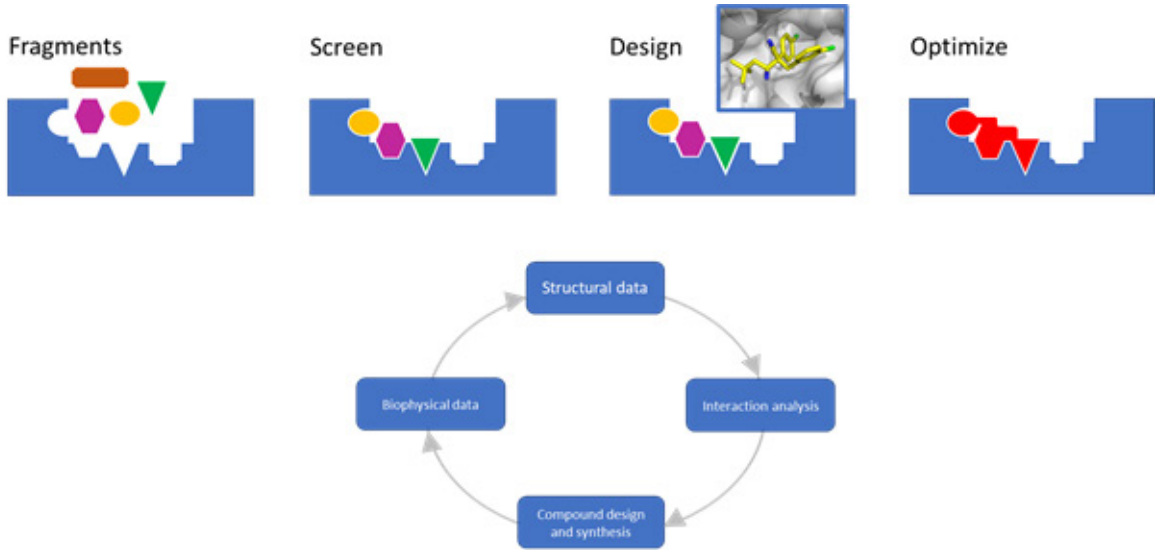

Figure 2: Schematic representation of fragment -based drug design. (Provided by Captor Therapeutics)

METHOD

Frozen protein crystals containing the targeted protein in combination with different ligands were measured at the High-Throughput Macromolecular Crystallography Beamline P11. The diffraction images were used to determine the structure of the proteins and ligands at an atomic resolution. Identifying suitable ligands for future drug application is then possible once the structure is known, since it shows whether or not a ligand and protein form a complex.

BENEFITS

An efficient crystallography platform at Captor Therapeutics, as well as regular and frequent measurements at the synchrotron PETRA III, have allowed several target protein complex structures to be generated. The precise structural data is guiding a rational drug design and resulting in significant improvements in the binding affinity and specificity of Captor products.
Structure-based drug design projects are very demanding, because they require high-resolution data and the analysis of many samples in a short space of time. The beamline P11 is ideally suited to this purpose: with fixed parameters, P11 allows up to 30 samples to be collected per hour.

INSIGHTS AND ANALYSIS

Rational drug design is the process of finding new drugs based on knowledge of a biological target. Drug design that relies on the knowledge of the three-dimensional structure of a target protein is known as structure-based drug design, a method that has been used successfully to improve the affinity, selectivity and stability of ligands that are to become drugs in later steps. For this purpose, it is necessary to employ well-diffracting protein crystals with bound ligands, obtain precise crystallographic data and determine the structure of the complex at a resolution that allows the protein-ligand interaction to be identified. Based on this information, scientists can then design a new and improved ligand and repeat the whole process from the beginning, as outlined in Figure 2. As a result of numerous iterations, it is possible to obtain a ligand which has the desired characteristics.

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