Abstract

This project includes a series of eight posters produced by the students in Biochemistry II. The purpose for the poster project is to explain the function of a specific pharmaceutical drug from several key perspectives. Each group of students selected a molecule that targets the activity of a specific enzyme and produced a poster describing its function. Collectively, the features of the poster provide a robust integration of advanced concepts and skills studied in Biochemistry II.

Mechanisms of Various Pharmaceutical Drugs

Students in Biochemistry II are juniors and seniors majoring in biochemistry, molecular biology, chemistry, or biology. Selection of an appropriate topic for their poster required finding an example of a drug that works by a reasonably well-known mechanism. Students needed to identify both a drug molecule and its target enzyme that would feature in the poster. To complete the protein modeling portion of the poster, students also needed to locate an entry for their target enzyme in the RCSB Protein Data Bank[1]. This is a repository of protein structure data collected by x-ray crystallography or nuclear magnetic resonance analysis.

Project Description

Each poster begins by introducing the drug or drug family and showing its structure, highlighting key chemical groups. The relevance of the drug as a therapy is established through a description of the biochemical or physiological pathway where the enzyme functions. Therapeutic molecules are frequently inhibitors of an enzyme that carries out a specific reaction. The role of the drug is defined more specifically by analysis of its interaction with a target enzyme within the pathway. A detailed explanation is provided using Protein Explorer, where a detailed explanation is provided of the drug interaction with its target and demonstrated through a student-generated protein model based on crystallography data using Protein Explorer. The specific topics of each poster are described below.

Bradykinin Potentiating Peptide b: Hypertension Treatment

J. Nick DiMino (Biology Senior) & Timothy Fair (Botany Senior)

The renin-angiotensin system (RAS) is an important pathway that regulates many biological processes, including blood pressure. A key step in this pathway is the production of angiotensin II (Ang II), which interacts with angiotensin receptors, and it can also raise blood pressure. Ang II is produced from angiotensin I (Ang I) by angiotensin-I converting enzyme (ACE). ACE is the target of many drug inhibitors because preventing the formation of Ang II can lower blood pressure. Bradykinin-potentiating peptide b (BPPb) is a unique ACE inhibitor because it targets just one of ACE's two active domains, the C-domain. It does so by binding in the same manner as Ang II through a number of hydrophobic interactions and hydrogen bonds (RCSB Protein Data Bank) (Hanson, et al., 2007).

Lodosyn (Carbidopa): Parkinson's Treatment

Cara Discavage (Molecular Biology Senior) & Moira Dougherty (Molecular Biology Senior)

Carbidopa is a drug, usually prescribed to those with Parkinson's disease, because it prevents the premature conversion of L-DOPA to the neurotransmitter dopamine via the enzyme DOPA decarboxylase (DDC). By inhibiting DDC, carbidopa decreases the amount of L-DOPA metabolised in the peripheral nervous system and allows for more L-DOPA to cross the blood-brain barrier into the central nervous system. L-DOPA is then converted to dopamine, leading to higher dopamine levels in the brain, which have been shown to help reverse symptoms of Parkinson's disease (RCSB Protein Data Bank) (Hanson, et al., 2007).

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Januvia (Sitagliptin): Diabetes Treatment

Cara Dombroski (Biochemistry Senior) & Melanie Snyder (Biochemistry Senior)

Individuals who suffer from Type II diabetes are unable to produce a sufficient amount of insulin for the body to survive, and the insulin that the body does produce is not as effective as in those without the disease. Januvia has been developed to help treat those with Type II diabetes. Also known as sitagliptin, this is an oral medication that helps control blood sugar levels by regulating insulin produced by the body and lowering the side-effects of low blood sugar (hypoglycemia) for individuals who have Type II diabetes. More specifically, this drug is an example of a class of antidiabetic drugs known as dipeptidyl peptidase-4 (DPP-4) inhibitors. These drugs reduce the amount of glucose in the body by manipulating hormones involved in glucose metabolism. DPP-4 inhibitors increase levels of the hormone incretin, which regulates the production of glucagon. Glucagon is a second hormone that functions to increase blood glucose levels by increasing insulin within cells and decreasing insulin resistance (RCSB Protein Data Bank) (Hanson, et al., 2007).

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Antogonists of the p53-Mdm2 Interaction to Treat Cancer

Katherine Geating (Molecular Biology Senior), Zachary Mansfield (Molecular Biology Senior) & Joy Thames (Biochemistry Junior)

Inactivation of the p53 tumor suppressor gene is responsible for over 50% of all human cancers. This inactivation includes mutations in this gene, as well as in genes responsible for regulation of p53, since they can cause a change in expression levels that lead to cancer. The Mdm2 gene is a regulator of p53 that is known to cause cancer by inhibiting expression of p53. Our project aims to illustrate work showing the use of two distinctive small molecule inhibitors in the p53-Mdm2 interaction. Small molecule inhibitors with 3-pyrrolin-2-one and 2-furanone structures have been designed to block the interaction between Mdm2 and p53 to allow normal expression of p53 and to prevent cancer. These small molecule inhibitors show promise as drugs for use in treating cancer (RCSB Protein Data Bank) (Hanson, et al., 2007).

Cipro (Ciprofloxacin): Antibiotic

Benjamin Grosso (Chemistry Senior) & Katelynn Nguyen (Biology Senior)

Ciprofloxacin is a broad-spectrum antibiotic and belongs to a class of drugs called fluoroquinolone antibiotics. This drug stops nucleic acid synthesis of bacteria by interfering with DNA gyrase. DNA gyrase functions to separate the double helix of DNA in order to replicate DNA. Without it, bacterial cells can no longer divide. Ciprofloxacin is good for enteric gram negative rods. It is used to treat UTI, intra-abdominal infections, systemic gram-negative

infections, gonorrhea, Haemophlus influenza, and Pseudomonas (RCSB Protein Data Bank) (Hanson, et al., 2007).

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Suramin: River Blindness Treatment

Ntajneeb Lo (Biochemistry Senior) & Alexander Parry (Marine Biology Senior)

Suramin is primarily used as a second-line treatment for early stage African Sleeping Sickness. Recent studies have shown that suramin and suramin derivative 8 are potential treatments for norovirus. The norovirus is a +ssRNA virus that causes gastroenteritis and potentially death. To date, no vaccines or drugs are known to treat norovirus and immunity is temporary. Norovirus is especially dangerous to children and the elderly, and it can spread easily in confined areas. Suramin 8 inhibits norovirus RNA-dependent RNA polymerase, which is required for replication of the virus. Suramin 8 has shown to have the same LC_{50} as suramin, but its lowered water solubility increases the potency of the drug against the norovirus (RCSB Protein Data Bank) (Hanson, et al., 2007).

Prinivil (Lisinopril): Hypertension Treatment

John-Paul Marrazzo (Biochemistry Junior) & Samantha Gillis (Biochemistry Junior)

Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor prescribed to patients with high blood pressure. It regulates blood pressure, and it treats hypertension and symptomatic congestive heart failure. Lisinopril specifically inhibits the conversion of angiotensin I (ATI) to angiotensin II (ATII). Formation of ATII triggers an increase in blood pressure. Lisinopril competes with ATI for binding to ACE and inhibits the change of ATI to ATII. It is an example of an ACE inhibitor that is a zinc metallopeptidase (RCSB Protein Data Bank) (Hanson, et al., 2007).

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Aromasin (Exemestane): Breast Cancer Treatment

Seth Martin (Biology Junior) & José Ureña (Chemistry Senior)

Exemestane (Aromasin®) is a steroidal drug and substrate analog that targets human cytochrome P450 aromatase. By binding more tightly than the usual substrate, exemestane can block the role the aromatase plays in the formation of estrogen. Elevated estrogen levels can contribute to unregulated cell growth. The drug is used to combat estrogen-dependent breast cancer in postmenopausal women through competitive and irreversible inhibition of aromatase (RCSB Protein Data Bank) (Hanson, et al., 2007).

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Conclusion

By exploring a specific example of a drug and its mechanism, students gain a greater appreciation for biochemical systems and pharmaceuticals. This project blends a study of detailed atomic-level interactions between the drug and its target enzyme. Furthermore, students connect the chemical functionality carried out by an enzyme with its larger role in cellular function or regulation of metabolic functions. There are a wide range of examples that provide a

suitable context for the project, allowing each group of students to study a drug that they have a special interest in.

References

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