



The Hunt for New Medicines

Uses of Information from the Human Genome: Therapeutic Drug Targets

Therapeutic drugs or medicines can prevent the development of disease, relieve symptoms, and save lives. Researchers are continually searching for new drugs, which are more effective, easier to administer, and have fewer side effects.

The search for new drugs is also big business. United States consumers spent \$154.5 billion dollars on drugs in 2001, and the number of visits to doctors involving drug therapy in 2000 was 545 million. The development of new, more effective drugs is a very active and potentially profitable field of research.

Drugs typically work on specific chemicals or targets in the body. Many targets are either enzymes or cell surface receptors that regulate chemical reactions. Approximately 483 drug targets account for nearly all drugs currently on the market. Researchers have predicted that the actual number may be several thousand. Because the human genome provides a rich source of information about newly discovered or predicted genes and gene products, it serves as a resource for finding possible new drug targets.

Paralogous genes – possible new drug targets:

Throughout human evolution there have been many duplication events within our genome. These duplications have led to the existence of paralogous genes – genes that have diverged after a duplication event within a species. Paralogous genes or paralogs typically have similar, though not necessarily identical functions. Hence, paralogs may provide possible new drug targets.

Serotonin receptors – a case in point: (from *Nature*)

Serotonin is a neurotransmitter that facilitates the transmission of signals between nerve cells. Serotonin has been shown to play a role in a number of medical conditions from migraines to depression to schizophrenia. Four of the 200 most commonly prescribed drugs in the United States are selective serotonin reuptake inhibitors (brand names: Celexa, Paxil, Prozac, Zoloft). These drugs are used to treat depression and anxiety disorders. They act on the serotonin receptor 5-HT_{3A}. Analysis of the draft human genome sequence revealed another serotonin receptor 5-HT_{3B}, which is thought to be another significant drug target for antidepressant/anti-anxiety treatment. Though the final outcome of the research is unknown, the discovery of this new receptor may lead to a wider range of medications to treat patients with anxiety and depression.

You will research the following drugs to serve as a starting point for searching out potential new drug targets. Each of these drugs is on the list of the 200 most commonly prescribed drugs in the United States. The gene for the specific target of each drug is in bold type within the paragraph. You will use the National Center for Biotechnology Information's database called LocusLink to search for paralogs of genes that code for these targets.

Lipitor

Lipitor is the most commonly prescribed drug in the United States. It is one of a handful of drugs known as statins. Its primary use is to lower cholesterol. People with high cholesterol are at greater risk for cardiovascular disease. Lowering cholesterol through drug therapy with Lipitor or other statins is believed to reduce a person's risk of heart attack or stroke. Lipitor acts on the enzyme, HMG-CoA reductase – **HMGCR**, which is essential in cholesterol synthesis. By inhibiting this enzyme, Lipitor reduces the amount of cholesterol synthesized in the body.

Target: 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase

Gene name: **HMGCR**

Lisinopril

Lisinopril is one of the most commonly prescribed drugs for high blood pressure in the United States. High blood pressure is a major risk factor for cardiovascular disease. Untreated or under-treated high blood pressure can lead to heart attack and stroke. Lisinopril belongs to a group of drugs known as ACE inhibitors. These drugs inhibit the angiotensin I converting enzyme – **ACE**, which is involved in a series of chemical reactions that cause blood pressure to increase. By inhibiting the angiotensin I converting enzyme, lisinopril lowers the patient's resting blood pressure.

Target: angiotensin I converting enzyme

Gene name: **ACE**

Prilosec

Prilosec is a drug used to treat frequent heartburn. Frequent heartburn is caused by stomach acid flowing out of the stomach and up into the esophagus. Over a period of time, the stomach acid can damage the esophagus and can eventually lead to esophageal cancer. Prilosec is a relatively new drug in the same class with Prevacid and Nexium. Prilosec works directly on an ion channel in the stomach lining, the ATPase, H⁺/K⁺ exchanging, alpha polypeptide – **ATP4A**. This ion channel plays an important role in maintaining the highly acidic pH of the stomach juices. The ion channel does this by pumping in H⁺ ions, which lower the pH. Prilosec blocks the activity of the ion channel and raises the pH of the stomach juices.

Target: ATPase, H⁺/K⁺ exchanging, alpha polypeptide

Gene name: **ATP4A**

1.) Open the homepage of the National Center for Biotechnology Information (NCBI) in your web browser.

<http://www.ncbi.nlm.nih.gov/>

- 2.) Click on **LocusLink** in the list of links in the far right column on the page.
- 3.) Type the Gene name of the target of your drug in the query field.
- 4.) In the pull-down menu next to the word “Organism”, select human. This will limit the search to human genes.
- 5.) Click “Go”.
- 6.) Click on the blue LocusID number in the far left column. You will get a detailed description of known information about the gene for this drug target. The description includes an overview, map information detailing the location of the gene, information about homologous genes in mice, domains found within the gene, and various links to the primary literature sources for this info (pm). You can refer to the handout “NCBI Website – Understanding the information on the Locus Link page”.
- 7.) At the very bottom of the page, you will see a section called “Related Sequences”. These are sequences in the human genome with high similarity to the gene for this drug target.

Click on each sequence in the “Nucleotide” column. We will focus on sequences in that column for the purpose of simplifying our search. Complete the table on the following pages for the drug target you are investigating.

How to interpret the information you get and what to look for:

- 1.) Many of the related sequences in this section are simply different entries in the sequence database of the same gene. You can generally ignore these since they represent multiple entries of the same sequence.
- 2.) Look for information about the function of the sequence by reading the description and the information about the journal article in which the sequence was published.
- 3.) DO NOT examine the actual sequence of base pairs. By itself, that will not give you any information about whether this sequence is a potential drug target.
- 4.) Look for information about whether this sequence is an alternative transcript or alternative splice product. If so, it could be a potential new drug target because it might code for a similar but slightly different version of the protein.
- 5.) Look for information about whether this sequence is a promoter region for your gene of interest. If so, it could be a potential new drug target because it might regulate expression of the gene.
- 6.) Look for whether the sequence is a similar sequence with unknown function. If so, it could be a potential drug target.
- 7.) Don’t worry about getting the exact right answer. Answers may vary slightly depending on how you interpret the information. Concentrate more on giving a good explanation.

Potential drug targets:

Lipitor:

Related Sequence	Description	Potential drug target? (yes/no/maybe/not enough information)	Explanation
BC024180	Homo sapiens, 3-hydroxy-3-methylglutaryl-Coenzyme A reductase, clone IMAGE:4824506, mRNA.	no	This is simply another version of the HMGCR gene
BC033692	Homo sapiens 3-hydroxy-3-methylglutaryl-Coenzyme A reductase, mRNA (cDNA clone MGC:45281 IMAGE:5212903), complete cds.	no	This is simply another version of the HMGCR gene
M11058	Human 3-hydroxy-3-methylglutaryl coenzyme A reductase mRNA, complete cds.	no	This is simply another version of the HMGCR gene
M62633	Human 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase mRNA, 3' flank	maybe	This is one of three size class variants of mRNA's transcribed from the HMGCR gene, suggesting that there are alternative transcripts that might produce slightly different proteins and hence possible different drug targets.

Lisinopril – ACE:

Related Sequence	Description	Potential drug target? (yes/no/maybe/not enough information)	Explanation
AF118569	Homo sapiens angiotensin I converting enzyme precursor (DCP1) gene, alternative splice products	yes	Alternative splice products are not different genes, but they may produce slightly different proteins that would be potential drug targets
AF229986	Homo sapiens angiotensin-converting enzyme gene, promoter region.	maybe	A promoter region would not code for a protein, so it would not code for a protein drug target; however, it might be possible to design a drug that would affect the promoter region itself and either up-regulate or down-regulate expression of the gene
BC036375	Homo sapiens angiotensin I converting enzyme (peptidyl-dipeptidaseA) 1, transcript variant 3, mRNA	maybe	Transcript variants are not different genes, but they could produce slightly different proteins (if they are translated) that would be potential drug targets
BM908180	cDNA	Not enough info	
J04144	Human angiotensin I-converting enzyme mRNA, complete cds	No	This is simply another entry of sequence data for the ACE gene derived from an mRNA
M26657	Human testicular angiotensin converting enzyme mRNA, complete cds	No	This is simply another entry of sequence data for the ACE gene derived from an mRNA from testicular tissue

M29981	Human aberrantly spliced angiotensin converting enzyme mRNA, complete cds	Maybe	This could represent an alternative spliced mRNA that might be translated into a protein that could be a potential drug target. We don't know if it is actually translated.
S81361	angiotensin I-converting enzyme [human, gastric HGT-1 cell line	No	This is simply another entry of sequence data for the ACE gene derived from an mRNA from stomach tissue
X16295	Human mRNA for angiotensin I converting enzyme (ACE)	No	If you look at the journal article summary that is referenced, you can read that in testicular tissue, a slightly different mRNA transcript is produced than in other areas of the body. While that may create a slightly different drug target, it would not be effective at controlling blood pressure (especially not in women) if it is only expressed in testicular tissue.

Prilosec:

Related Sequence	Description	Potential drug target? (yes/no/maybe/not enough information)	Explanation
AD000090	Homo sapiens DNA from chromosome 19q13.1 cosmid f14121 containing ATP4A and GADPH-2 genes, genomic sequence	no	This is a genomic sequence submitted to GenBank, which contains the ATP4A gene plus the GADPH-2 gene.
J05451	Human gastric (H+ + K+)-ATPase gene, complete cds.	no	This is simply another version of the ATP4A gene
M63962	Human gastric H,K-ATPase catalytic subunit gene, complete cds.	no	This is simply another version of the ATP4A gene
AK058032	Homo sapiens cDNA FLJ25303 fis, clone STM07904, highly similar to POTASSIUM-TRANSPORTING ATPASE ALPHA CHAIN (EC 3.6.1.36).	yes	This is a sequence highly similar to the alpha chain of the ATPase, so it could code for a similar protein that might have a similar function
AL832971	Homo sapiens mRNA; cDNA DKFZp666G172 (from clone DKFZp666G172)	Not enough information	

Extensions:

I. You are a research scientist for a major pharmaceutical company. Choose one of the drug targets you researched using LocusLink. Write a brief proposal to the head of your division for funding to pursue research on the drug target or targets that you identified from the human genome sequence. Include the importance of drugs that might be developed, how you identified this possible new target, and the potential financial benefit to your company.

II. Go to the list of the 200 most commonly prescribed drugs

<http://www.rxlist.com/top200.htm>

Research a drug that you are interested in to find its target. Use LocusLink to look for paralogs to the gene for this drug target.

To research your drug, you can use Google (www.google.com) to find the manufacturer's page for the drug. You can also go to the Medline Drug Information page (<http://www.nlm.nih.gov/medlineplus/druginformation.html>). Look for information on how the drug works. Sometimes this is found in sections on information for MD's.