

## New Drug Discovery in the Postgenomic Era: From Genomics to Proteomics

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**Issue:** *Now that the human genome is nearly completely mapped, new drugs in psychiatry will be increasingly based on mimicking or blocking the proteins expressed by these genes.*

**T**he Human Genome Project is the monumental task of mapping all the millions of DNA base pairs in tens of thousands of human genes on 24 chromosomes, known collectively as the *genome*.<sup>1,2</sup> It seems that genes may constitute only 3% of this DNA. The rest of the DNA is not well understood and is sometimes called “junk DNA,” although it is obviously there for reasons that will undoubtedly be clarified in the future. Nearly complete, the Human Genome Project may in some ways be obsolete before it is even finished because the complete picture of a cell is actually determined by the *proteins* expressed by these genes at any one time. The complete list, an amino acid sequence, of all the cell’s proteins is called the *proteome*.

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### EXPRESS YOURSELF

Genes express proteins. Although there are estimated to be between 35,000 and 100,000 genes, the number of proteins expressed from these genes is far greater, perhaps millions. This is due to the fact that not only do many genes express multiple proteins, but also, many proteins can be modified or edited into multiple new proteins after they are expressed. For example, in previous BRAINSTORMS articles, we have discussed how multiple neurokinin peptides such as substance P can be synthesized from the same gene.<sup>3,4</sup>

Mapping the multitude of proteins ultimately expressed by the human genome, i.e., the human proteome, will be a much more laborious task. Nobody really knows how many proteins there are, and since protein modifications can evolve, there may not even be a fixed number of cellular proteins. We may thus never have a complete map of the human proteome as we are about to receive for the human genome.

### CUT! CAMERA, TAKE TWO. ACTION!

Genes are first transcribed into RNA before they are translated into proteins. Sometimes the RNA is “ed-

ited” or revised by cutting and pasting, like revising a motion picture to insert a better take for a given scene. This process is called “splicing” of the RNA and therefore leads to different versions of RNA, and consequently to different versions of the protein. In other cases, the completed protein is subsequently modified by having pieces added or removed over time in a process known as posttranslational modification. Just how many times this can happen to a protein with the same genetic starting point is unknown.

### PHARMACOGENOMICS

One practical dividend of the Human Genome Project may be the ability to predict someday how a specific individual may respond to a given drug. It is well recognized, for example, that some patients respond to one antidepressant better than to another<sup>5,6</sup> and that some patients develop tardive dyskinesia when given neuroleptics whereas others do not.<sup>7</sup> The expectation is that a specific genetic makeup is responsible not only for responding to the therapeutic actions of a drug but also for developing side effects to that drug. By gaining an understanding of this re-

lationship, we may someday be able to have our key genetic information on a computer chip that can be read to match the best drug to our specific needs.

Whither pharmacoproteomics? It may also be possible to identify abnormal gene products (i.e., abnormal proteins) or the lack of formation of normal gene products (absent proteins) when studying the proteome of a neuron from a patient with a psychiatric disorder. Many psychiatric illnesses are thought to be the product of “complex genetics”<sup>2</sup> in which multiple genes are involved, including inherited abnormal genes as well as the malfunction of normal genes perhaps caused by abnormal environmental input. Thus, identifying key disease-related proteins may help diagnose various illnesses and also predict which drug will have the best effect in a given individual.

#### TARGET PRACTICE

Of all the drugs in the modern pharmacopoeia, there are perhaps 500 or so drug targets, generally enzymes or receptors. Now that there are conservatively 500,000 or more potentially important proteins known or suspected to be expressed by the human genome, suddenly there are 1000 times more targets for drug development than we have known since the beginning of time. This provides an incredible opportunity for expanding the pharmacopoeia, because chemists can theoretically make highly selective substitutes or blockers of any known protein. The bigger problem is which protein to target. The answer lies in gaining an understanding of how proteins normally mediate neuronal functioning and how failures in their actions lead to psychiatric disorders.

The logical starting point for key target proteins is, of course, with re-

ceptors and enzymes, just as it has been throughout the history of drug development. However, other targets are increasingly emerging, such as the proteins involved in signal transduction pathways, namely, those proteins that mediate the cascades of messages from the receptor to the genome and from the genome to protein synthesis. Thus, second-messenger systems, protein kinases, phosphorylated substrates, transcription factors, and ion channels are suspected to be likely mediators of neuronal disorders and therefore likely targets for new drug development. As the proteins that regulate these cellular processes are clarified, they can be studied in various disorders to determine whether they are appropriate targets for new drugs. Studies are needed to provide tips not only on which proteins to target with new drugs, but on whether the protein function should be mimicked or blocked.

#### SUMMARY

We have entered an exciting new era in which the nearly completed mapping of the human genome is now leading to the ability to charac-

terize the human proteome, thereby expanding the horizon for new drug development by 3 orders of magnitude. Figuring out which proteins are involved in which disorders and in which individuals with any given disorder holds the promise of highly individualized therapeutics in the not so distant future. ♦

#### REFERENCES

1. Stahl SM. *Essential Psychopharmacology*. New York, NY: Cambridge University Press; 2000
2. Hyman SE. Introduction to the complex genetics of mental disorders. *Biol Psychiatry* 1999;45:518-521
3. Stahl SM. Peptides and psychiatry, pt 1: how synthesis of neuropeptides differs from classical neurotransmitter synthesis [BRAINSTORMS]. *J Clin Psychiatry* 1999;60:5-6
4. Stahl SM. Peptides and psychiatry, pt 2: substance P and the neurokinins: novel peptide neurotransmitters in psychopharmacology [BRAINSTORMS]. *J Clin Psychiatry* 1999;60:77-78
5. Stahl SM. Placebo controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. *Biol Psychiatry* 2000;48:894-901
6. Siever LJ. Antidepressant selection in the postgenomic era. *Biol Psychiatry* 2000;48:875-877
7. Segman R, Neeman T, Heresco-Levy U, et al. Genotypic association between the dopamine D<sub>2</sub> receptor and tardive dyskinesia in chronic schizophrenia. *Mol Psychiatry* 1999;4:247-253

#### Take-Home Points

- ♦ Genomics in psychiatry is the study of how genes control normal neuronal function and how psychiatric disorders may result from abnormal gene function.
- ♦ Pharmacogenomics is the study of how different genes may specifically predict an individual's responses to a drug, such as side effects and therapeutic effects.
- ♦ Proteomics is the study of the different proteins expressed by the genome, sometimes several proteins to a single gene. A major strategy for the discovery of new drugs is to either mimic or block the actions of these proteins.