Pharmaceutical Research, Vol. 15, No. 7, 1998

Commentary

Genomics and Drugs: Finding the Optimal Drug for the Right Patient

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Received March 13, 1998; accepted April 14, 1998

INTRODUCTION

Sequencing the first complete genome, *Hemophilus influenzae*, in 95 (1) reminded us that the complexity of cellular organisms is finite, at least in its number of genes. Further, it teaches us to study all genes and their genomic organization together, rather than singly, in a new scientific field termed genomics. Meanwhile, the number of fully sequenced genomes exceeds 10, covering all three of the great phyla of cellular life, bacteria, archaea, and eukaryotes. While the number of genes in a prokaryote is estimated in the range of 500–1,500, yeast as the first fully sequenced eukaryote (2,3) contains approximately 6,000 genes. There are commonalities among all cellular life forms; however, the number of genes unique to any of the phyla is also surprising. Much work remains before we understand the functions of all genes in a living organisms, let alone their interactions among each other.

Among the genomic sequencing efforts, the human genome project stands out as the ultimate challenge. With 3 billion base pairs and approximately 75,000 genes, this gargantuan enterprise was initially berated by skeptics as a futile exercise. Presently, few scientists continue to oppose the pursuit of this goal which may be completed within 5–10 years. Of course, individual genomic sequences will differ to the extent of 1 in 1,000 bases, thereby, generating a nearly infinite number of variations. By searching for mutations we will be able to understand the molecular genetic basis of diseases. Thus, genotyping individual patients, in addition to phenotyping target tissues such as cancers (by measuring all expressed mRNAs or proteins (the proteome (4)), could lead to better diagnosis and therapy. Even though only a few thousand human genes are fully sequenced at this time, we already have some information on possibly over 90% of all human genes, and countless more in other species throughout the tree of life. This information exists in the form of 'expressed sequence tags' (EST's): by large scale partial sequencing of mRNAs (in their cDNA form) one rapidly obtains sequence fragments representing expressed genes in the tissue analyzed (5). Currently, the public databases contain 2 million EST's, with commercial databases exceeding this number several-fold.

With an exponential growth of the sequence database, novel approaches are needed to benefit from this vast newly available information. This is the goal of bioinformatics, the science dealing with management and integration of information on sequence, structure, and function. Within a few years, genomics and bioinformatics have taken center stage in the biosciences, and any pharmaceutical company of repute is establishing a strong effort in this area. I will attempt to analyze here what genomics might mean for drug discovery, development, and clinical application. How academia and industry have to adapt to the challenge of providing properly trained scientists and reorienting global research directions is implicit in this discussion.

FINDING NEW TARGETS FOR DRUG DISCOVERY

Most obvious among the potential benefits derived from genomic sequences is the ability to select genes as novel drug targets. When the genomic sequence of *Helicobacter pylori* was published (6,7), one could ask which of the approximately 1,000 putative genes might serve as a suitable target for chemotherapy. Since *H. pylori* has been recognized as a causative agent in gastric ulcers, antibiotics have replaced antihistamines as the major treatment of ulcers, and a highly effective treatment would be of enormous value. Such a broad approach requires large resources, and novel technologies are required to screen large numbers of compounds against many targets. This challenge, in addition to cost savings, is one of the incentives for the current flurry of mergers among major pharmaceutical companies to permit the sharing of their individual resources (8).

The availability of large numbers of compounds is realized through combinatorial chemistry, i.e., the parallel, rather than sequential, synthesis of many chemicals from several fragments, each with multiple structural modifications (9,10). First chemically synthesized libraries were peptides consisting of the 20 natural amino acids, imitating nature's way of generating a nearly infinite number of distinct proteins from simple precursor molecules. This concept has now expanded to include organic chemicals synthesized in parallel from small building blocks, or it is based on biological processes such as phage display (11)

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0724-8741/98/0700-0959$15.00/0 © 1998 Plenum Publishing Corporation

and combinatorial biosynthesis (12,13). Because the chemical structure of the backbone is invariant for most libraries, overall structural diversity may be limited in any single library. Thus, screening of natural products for active ingredients may continue for some time to come, but one would expect that the diversity between different chemical libraries will soon satisfy most requirements for drug discovery.

Dealing with many samples rapidly has also become feasible with the use of high-throughput-screening, or HTS (14). By miniaturizing reaction volumes into the microliter or even nanoliter range, achievable by using novel nanotechnologies, thousands and even millions of samples can be analyzed in short time periods. Often these screening methods employ biological systems for analysis, for example engineered yeast strains such that each yeast cell becomes its own reaction vessel (14,15). The applicable technology is extremely diverse, and an entire industry has developed around HTS.

Less certain approaches deal with the question of how to select the optimal target genes, and in this point, predictions for the future development of drug discovery begin to diverge. One might naively assume that with the sequencing of the human genome, one gains as many new drug targets as there are genes. However, by defining the question more narrowly, e.g., how many single gene targets (proteins) exist in the human genome that determine a disease process *and* can be targeted for effective therapy of a major disease (i.e., afflicting a large patient population), *and* have not already been discovered, the number is much lower, maybe less than 1,000 or possibly even below 100 genes. Moreover, many of the major chronic diseases (cardiovascular and mental disorders, and cancer) are multigenic in origin, and finding a single critical gene for drug targeting is difficult or may not be possible. On the other hand, in the treatment of infectious diseases, a large number of new microbial genes as drug targets is likely to emerge, and this area will blossom rapidly. Yet, an overly optimistic assessment of the number of useful drug targets, revealed through genomics, could prove disastrous to the pharmaceutical and biotechnology industry. Much more thought needs to be given to sound approaches in drug target identification.

LEARNING FROM GENOMICS ABOUT RECEPTOR STRUCTURE AND DRUG DESIGN

Comparison of human genes with those from other species can provide valuable information. Often, protein structure, and hence function, are highly conserved even though mutational drift has led to considerable sequence divergence. This can be exploited in a number of ways in drug discovery and design. Because yeast mutants lacking specific genes are readily obtained by genetic methods, yeast has been used to search for human orthologs (homologous genes with the same function in another species) capable of functionally substituting the missing yeast gene. Despite an evolutionary distance of approximately 800 million years, at least seventy human genes have now been identified that are functional in yeast, first among them the *H-ras* gene (2). This has resulted in complementation cloning of several human genes associated with diseases, including the neurofibromatosis gene NF1. Moreover, complementing mutant yeast with human genes can serve to develop HTS systems, for identifying lead compounds from combinatorial libraries (14,15).

The extraordinary conservation of protein structure, but not necessarily sequence, over a large evolutionary time span can further serve as the basis for developing three-dimensional structural models of mammalian proteins from known structures of distantly related proteins, determined by X-ray crystallography. For example, bacterial periplasmic binding proteins represent a large gene family responsible for sensing the environment for bacterial chemotaxis and scavenging nutrients. From the available crystal structures in the presence or absence of their ligands, one can deduce structure of the binding pocket and mode of ligand binding with subsequent rearrangement of the binding protein (16). In the process of evolution, these periplasmic binding proteins have fused with a number of genes encoding neurotransmitter receptors. For example, the large extracellular N-terminus of the metabotropic glutamate receptors (mgr's, heptahelical receptors coupled to G proteins) appears to be homologous to periplasmic binding proteins (17). Therefore, O'Hara et al. (17) have built a homology model of the N-terminus of mgr1 which accurately defines the putative glutamate binding pocket and can serve as a starting point for computer assisted drug design. Similarly, the ionotropic NMDA glutamate receptors (excitatory neuronal ion channels, and a major target receptor for drug design) contain an extracellular module derived from the periplasmic binding proteins, that has been modeled by homology (18). This accounts for the finding that glutamate activates two entirely different classes of receptor families.

These results suggest that the same modules might recur in additional receptors of pharmaceutical relevance. We have developed an iterative sequence analysis procedure (INCA: iterative neighborhood cluster analysis. See: http://itsa.ucsf.edu/~gram/home/inca/index.html) (19) which enables us to perform a comprehensive search of the available databases for additional homologs. Indeed, the periplasmic binding proteins appear to serve as binding domains for several additional receptor types, including the GABA-B receptors (G protein coupled receptors) (20), and hence, the binding domains of major excitatory and inhibitory neurotransmitter receptors are each related to each other by evolution. This example highlights the parsimony of nature in utilizing common modules to generate diverse functional proteins, and it suggests new approaches in drug design on the basis of structural homology.

Presently, the number of cloned and sequenced genes far exceeds those where the structure has been determined by X-ray crystallography. For the latter, new drug leads can be suggested by computerized docking of large libraries of chemicals with known structure (21). Therefore, homology modeling of 3D structures could become extremely useful in drug discovery, provided the homology models are accurate. However, our understanding of protein folding and ligand binding is incomplete as yet, and we must wait for further advances before this strategy can be successfully implemented on a broader scale. Further, this appoach competes with random screening of large numbers of chemicals using extremely fast HTS systems.

LIMITATIONS OF DRUG EFFICACY

Gene duplication can occur by several mechanisms during evolution (2), generating biological diversity and redundancy, with profound implication for drug discovery and therapy. The large superfamily of G proteins coupled receptors alone contains

possibly 2,000 related human genes. Each of these encodes a neurotransmitter/hormone/odorant/pheromone/ion receptor with distinct functions; however, because of similarities in primary structure and molecular architecture, it is exceedingly difficult to design specific drugs that do not cross-react among several receptors. Indeed, a drug cannot be considered 'specific' for a given receptor even if one has screened its binding to 20–30 receptors without detecting any cross-reactivities. At best, 'selective' is a more appropriate term until much more work is done to exclude other receptor interactions. Similarly, transporter and ion channel gene families count thousands of members; thus, there are numerous potential targets for drug discovery, but also a high probability for promiscuous binding of drugs to multiple proteins. Multiple cross-reactivities as an *expected* characteristic of small molecular weight chemical drugs could limit efficacy over a large patient population. The robustness of biochemical signaling pathways could pose another problem: disturbing a single step in a highly regulated signaling or reaction cascade may have only minimal effects on the overall pathway (22). Lastly, and perhaps most importantly, individual genetic diversity limits the patient population that can be successfully treated with any given therapeutic regimen. Hence, biological redundance, robustness, and diversity are relevant to the design of new drug therapies and for evaluating its ultimate limitations.

PHARMACOGENOMICS AS A SUBSPECIALTY OF BIOINFORMATICS

Even the most successful drug therapies provide optimal benefits only to a portion of the treated patients whereas some patients may gain no benefits, and others may experience undue toxicity. 'No single drug fits all patients' is the emerging motto. As many diseases are multigenic, different gene products may be the most suitable drug targets in subpopulations of patients diagnosed with the same disease. From the preceding discussion, we further expect that each drug has the capacity to interact with multiple endogenous proteins, including receptors, transporters, metabolizing enzymes, binding and carrier proteins, and structural proteins, most of which are not directly linked to the disease. Each of these factors can modulate drug effects *in vivo*, and therefore, could represent a determinant of drug efficacy or toxicity. Considering all protein classes together, we could estimate that on the order of 20 proteins represent the main efficacy determinants for a given drug in an individual patient. Moreover, there may be several alleles for each gene distributed among the human population, each of which encodes a protein with potentially distinct drug interactions. As a result, we should anticipate 100 or more variables as possible genetic determinants of single drug therapy, in addition to environmental factors, such as diet and smoking. At this point, the new field of pharmacogenomics comes into play (23). Previously, pharmacogenetics has focused on a single gene and its allelic distribution in the patient population. Now, a much broader approach encompasses multiple genes and their alleles, to define disease states in target tissues, and expected susceptibility to drugs in all tissues.

The technology to address such large scale questions has progressed at lightning speed. Microarray chips capable of detecting 400,000 individual gene fragments on a 1,6 cm^2 surface are getting close to the task of simultaneously assaying all human genes (23). Amazingly, combinatorial synthesis of the oligonucleotides, based on laser photolithography, can produce thousands of probes placed directly in the same microarray chip, without additional cost for greater complexity. Several other approaches also permit the wholesale assay of genes or mRNAs, including SAGE (serial analysis of gene expression) (24–28). Thus, one can ask which genes are overexpressed and which ones are underexpressed in cancer tissue versus the surrounding normal tissue (4), leading to the discovery of potential oncogenes and tumor suppressors, respectively. Technology to determine the entirety of expressed proteins, the proteome, are also emerging (4). Hence, the technical know-how is already at our disposition, available for use in pharmacogenomics.

Among the first entries in this area are the microarray chips of Affymetrix for the simultaneous analysis of the cytochrome P450 enzymes and their alleles (29,30). Major enzymes of drug metabolism, the large gene family of P450 oxygenases is a determinant of duration of drug action, and often drug toxicity. Poor metabolizers of certain drugs lack functional P450 isotypes and may be at risk of toxicity. Therefore, genotyping patient for their P450 alleles can assist in the selection of the appropriate drug for an individual patient. Similarly, there may be as many as 2,000 genes encoding transporters, many of which play a role in drug disposition and targeting. Therefore, expression of transporter genes and their mutant alleles can be expected to affect drug efficacy significantly. For example, oral therapy with cephalosporins may be ineffective if the requisite dipeptide transporter responsible for intestinal absorption (31 and refs. therein) is inactive or absent. Thus, I envisage development of a transporter microarray assay for the genotyping and phenotyping of drug transporters in tissues of individual patients. Alternatively, transporter phenotyping in cancer tissues could serve for the targeted delivery of anticancer drugs (e.g., 32). Because of our limited current knowledge on drug transporters, not to mention any alleles of transporters that might have altered drug transport characteristics, this certainly will require a large scale international effort among many laboratories interested in drug transporters.

FINDING THE RIGHT PATIENT FOR A GIVEN DRUG

Given the complexity of all factors relevant to therapy, medical information sciences (MIS) have emerged as an area of great promise in optimizing therapy. While MIS includes all clinical aspects of therapy and disease outcome, the application of pharmacogenomics could grow into a strong component of the therapeutic management of individual patients (23). This is particularly evident for cancer chemotherapy where response rates, and certainly cure rates, are limited. Often, cancer chemotherapy is curative only in a small fraction of the treated patients, and therefore, predicting correctly the therapeutic outcome for individual patients would offer dramatic improvements of anticancer therapy. Failure or success is determined at least in part by the genetic makeup of the tumor and the patient, a complex problem currently beyond practical reach. Yet, large scale genotyping and phenotyping could yield new insights into the crucial determinants.

Ability to focus on just a few genes initially, permits an entry into pharmacogenomics with well defined objectives. For

example, by measuring allelic distributions of the main P450 enzymes responsible for the metabolism of most drugs, one finds that each is represented by only a few major alleles relevant to variability of drug metabolism (29). Hence, one can solve and simplify a portion of the overall problem, and then focus on the next most likely factors, thereby, gradually enhancing the predictive power of pharmacogenomics. Successful prediction of which patient is likely to benefit the most from a given drug regimen, would represent a quantum leap in drug therapy.

ROLE OF PHARMACOKINETICS/ PHARMACODYNAMICS

Measuring quantitatively the absorption, distribution, metabolism and excretion of a drug from the body, and further, its interaction with the receptor and the resultant response or toxic effect, is the subject of pharmacokinetics/pharmacodynamics (PK/PD). Insights into how the drug behaves in the body and what controls its ultimate effect have already had a strong impact on drug therapy. In particular, variations of pharmacokinetic and pharmacodynamic parameters in a patient population can be assessed quantitatively. This offers the opportunity to explore the main determinants of variability in drug response among individual patients, and it has been used to optimize individual therapy. Since PK/PD reveals whether variability for a given drug arises primarily from metabolism, distribution, or receptor interactions, pharmacogenomic analysis can focus on those gene products, such as metabolizing enzymes, transporters, or receptors, that affect the drug's response most dramatically. Conversely, the ability to genotype a patient would permit a more accurate PK/PD analysis of a targeted patient population. Such PK/PD-pharmacogenomics interactions could result in better predictability of therapeutic outcome.

PREDICTING FUTURE TRENDS

In a rapidly changing world, it is dangerous to guess future trends in drug therapy. However, outlines of the new era of genomics are already discernible in broad strokes, and its impact on therapy can be gauged to some extent. Newly discovered target genes will lead to improved diagnosis, early intervention, and a host of novel drug therapies. This will further accelerate once strategies for identification of optimal drug targets have improved. Developing a new drug into clinically useful therapy will be aided by defining additional genes that affect drug efficacy, such as cross-reacting receptors, transporters, and metabolizing enzymes. However, biological redundancy, diversity, and robustness could pose a limit on the ultimate efficacy of traditional small-molecular-weight drugs, no matter how good the primary drug target. As a result, no single drug will serve all patients best. Thus, the modern era of discovering 'blockbuster' drugs based on novel targets builds on a finite number of suitable human target genes. Given the enormous costs presently incurred in the development of a new drug, a large number of patients must be treated to recover costs. Eventually, costs will exceed potential returns, and the ongoing boom in new drug development could collapse. Therefore, drug discovery must begin to focus on new goals over the next 10–20 years. By substantially reducing costs, pharmaceutical companies could turn to developing therapies against diseases afflicting much smaller patient populations, integrated with genomic diagnosis and prevention. Given the likelihood that most of the major chronic diseases have a multigenic etiology, small sub-populations of patients will emerge also within the major disease groups that respond uniquely to a specific drug.

To permit the development of drugs targeted to small patient populations, economic, legal, and ethical issues need to be reexamined from the ground up. The cost of drug discovery can be reduced by taking advantage of the new technologies described herein. Moreover, the therapeutic risk/benefit ratio can be more accurately assessed for a well defined patient population. By excluding marginally responsive patients from therapy with a given drug, risk of adverse effects would be limited to those patient most likely to benefit from it. This could permit one to streamline regulatory requirements for new drug approvals, designed to assure public safety. As a result, additional cost savings could be possible by scaling down clinical phase I-III trials. Finally, widespread diagnosis of genetic susceptibility to disease raises serious ethical questions related to individual rights, such as the right to privacy, and these must also be resolved in public debate.

Recognizing biological diversity and redundancy as limiting factors of drug efficacy over a large patient population, pharmacogenomics can direct drug therapy, by selecting the optimal drug for an individual patient. Once this strategy is implemented and successful to its full potential, one could greatly improve drug therapy with the currently available drugs, and any future novel drug entities would further expand successful therapy. This could dramatically reduce overall drug use, such as that associated with multidrug medication of doubtful value, yet so prevalent among the elderly.

As fine-tuning drug therapy could play and increasing role, one can also expect that pharmaceutical formulations will remain a key element of successful therapy. By controlling drug release and targeting in the body, additional therapeutic benefits can be attained. This often comes at significantly lower costs than the development of new drugs.

This overall scenario could dramatically change with breakthroughs in other treatment modalities. These include the use of proteins or oligonucleotides as drugs, gene therapy, tissue engineering, and novel approaches in vaccination, using either protein antigens or DNA encoding antigens. The development of protein drugs has already gained a major stake in therapy, whereas other modalities remain largely experimental. Clearly, protein drugs, such as erythropoetin and GM-CSF, represent major additions to our therapeutic armamentarium, but protein drugs in general also have limitations of their own. The question of what role these therapies will play in the long term cannot presently be answered with any degree of accuracy. Indeed, the future success of therapy with conventional drugs, or rather its inherent limitations, will play a critical role in the emergence of novel therapeutic modalities.

CONCLUSIONS

We are likely to see a boom in the development of novel drugs over the next 10–20 years. This could be followed by a decline of the rate of new block-buster drugs reaching clinical use. Further drug development should focus on well defined smaller patient populations, provided that costs can be drastically reduced. Pharmacogenomics (as part of medical information sciences) will improve therapy by defining the

optimal patient population most likely to benefit from a given drug treatment. Additional costs of routine pharmacogenomics will be more than compensated for by cost savings from improved therapy. Optimizing drug formulations will continue to play a key role in drug development. More effective therapy could lead to a drastic reduction in drug consumption without loss of therapeutic care. These changes could have profound effects on the future direction of the pharmaceutical industry and the focus of the pharmaceutical sciences.

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