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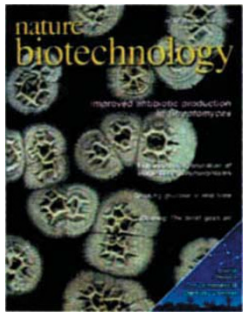
In defense of genomics

To the editor:

Rarely do we feel compelled to comment on articles we read in the pages of *Nature Biotechnology* or any other journal. The commentary by Larry Gold and Joseph Alper (*Nature Biotechnology* 15:297, April 1997) entitled "Keeping pace with genomics through combinatorial chemistry" is an exception since it is misleading in several respects and does the genomics industry an unnecessary disservice.



The authors submit that genomics will provide too many potential targets and that many of these will not be real targets and will result in wasted effort going up "blind alleys" that have "no impact on disease progression." They contend that "the antisense approach is an example of a target validation paradigm that provides drug candidates more or less instantaneously." In addition, Gold and Alper are promoting the notion that aptamer technology can be used to "go directly to a drug that produces a useful biological effect and skips target identification altogether." We would like to examine these statements and demonstrate that, as they state, their "less rational approach" is just what they call it.

Recent drug discovery, which has resulted in less-than-impressive returns on investment for the pharmaceutical industry as a whole, has occurred in part because the new targets, many of which were derived from the results of molecular cloning, have not turned out to be accessible points of intervention. In essence, drug discovery and development has been stifled by the paucity of information pertaining to the biochemical pathway(s) in which a target functions or to the best point of molecular intervention, as defined by the pathway.

Genomics has its origins in the human genome project, the initial intent of which was to map, sequence, and characterize all human chromosomes in order to facilitate more effective discovery of genes involved in disease and other biological processes. Since that time, it has rapidly evolved from this genetic focus to encompass a much wider set of disciplines in biology. This growth has resulted in an explosion of advances in both information and technology. Genomics now encompasses large-scale sequencing of genes and entire genomes (like those produced by Merck-WUSTL, TIGR, Incyte, and others), in depth comparative analysis of these sequences, gene expression analysis using arrays and other techniques, positional cloning of disease susceptibility genes, and biochemical pathway discovery using a variety of methods, including the use of such model organisms as the nematode worm *Caenorhabditis elegans*.

The great interest in genomics derives from the fact that genes found to be involved in the pathology of (or susceptibility to) a disease are validated as targets well ahead of expensive lead discovery research The recent discovery of mutations in the presenilin genes that cause early-onset Alzheimer's disease (AD) in certain families[1-3] provides an object lesson in the power of positional cloning in helping to unravel disease pathology and in providing novel points of intervention.

Most groups aiming to discover disease-modifying agents for AD are examining presenilin gene function and attempting to elucidate the pathway in which these proteins function. Neither of these genes, nor the importance of ApoE4 in late-onset AD, would have been evident without genetic analysis. Moreover, it now appears that the ApoE4 status of individuals affects response to drugs affecting cognition[4,5]: Different alleles of the presenilin genes may have a similar effect. Similarly, understanding the defect in the cystic fibrosis transmembrane regulator (CFTR), different alleles of which cause cystic fibrosis, is leading to new ways of treating the disease by altering the function of other sodium or chloride transporters[6,7].

There are very few data to suggest that aptamer technology can be used successfully to find acceptable drug leads, particularly in the absence of a defined drug target. There is no question that the technique can be used to develop molecules that bind targets with high affinity and there is little doubt that NeXstar and others can find pools of molecules that bind tightly and specifically to a target protein in a week. But this is a far cry from a drug candidate—let alone a way of validating any target. It is well known that going from a modified oligonucleotide that works in vitro to an effective in vivo agent is a long and uncertain road. It is also well known that peptide and oligonucleotide leads are notoriously difficult to turn into any sort of drug candidate. The real power of combinatorial chemistry lies in the ability to make libraries of related heterocyclic compounds with acceptable logP and low molecular weight for screening or lead optimization. The aside that "at least the validating (antisense) compound can serve as a benchmark for further drug discovery efforts" (meaning, we assume, screening for more reasonable therapeutic molecules) is much more likely to represent the rule rather than the exception. We see no new paradigm here, nor even the ability to keep pace with genomics in terms of target validation. The paradigm shift comes in fact from the ability to expand the use of genetically accessible systems, such as *C. elegans*, to define gene function and elucidate the relevant biochemical pathways—at least to the extent necessary to define a potential point of intervention. The discovery of the genes involved in early-onset type-2 diabetes (MODY) for example, points to the fact that transcription factors may be important control sites for glucose regulation, something that would not be readily evident from prevailing data[8,9].

We know of no genomics company that "trumpets genomics as the only solution." Sequana has always recognized that it is the combination of genomics, combinatorial chemistry, and screening that will drive drug discovery in the future. The authors are advocating unhealthy recidivism in drug screening by "skipping target identification altogether." The power of genomics, and positional cloning in particular, is to define targets and target pathways and to understand rapidly what the effects of modulating these targets will be. Functional screening of combinatorial libraries in the way advocated by the authors is indeed a "return to medicine before the molecular age" and should not be undertaken by anyone. The idea that "with aptamers in hand target identification proceeds quite simply" is revealing in its naiveté and totally without supporting data.

Genomic strategies do sit on the path to rational intervention. This is the way the drugs of the future will be discovered. There is no way that drugs that modify the pathology of schizophrenia or bipolar disease will be discovered without an understanding of the biochemistry underlying the disease process. Most of this information will be discovered by understanding the genetic basis of disease as has been attempted for AD. Sequana does not consider this in any case to be a mutually exclusive strategy. Serendipity is important. But this does not mean continually shooting in the dark by doing functional screening with compounds that will never become drugs.

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Gold and Alper reply:

We called our article "Keeping pace with. . ." rather than "Beating the daylights out of. . ." We and Harris/Buckler agree (and we wrote) that a rational attack on biology and disease includes genomics, functional genomics (expression measurements of many/most genes in normal and diseased tissues), model organisms, pathway analyses (including yeast two-hybrid experiments and classic enzymology), and subsequent drug development through all the powerful methods that smart people have developed. We were driven by Jürgen Drews' thoughtful article (*Nature Biotechnology* **14**:1516, November 1996) to consider the speed required to keep pace with genomics, and merely reiterated Drews' call for robust drug discovery tools (fast, as little medicinal chemistry/analoguing/optimization as possible, good performance in animals, etc). Many target candidates will be irrelevant to disease and thus target validation in animals (which is aided by genetics, biochemistry, model organism research, as well as fast drug discovery) is one key to useful information from genomics; no disagreements here, including their pointed remarks about the value of *C. elegans*—we still read the bacteriophage T4 literature as a model for herpes viruses.

We do disagree gently with Harris/Buckler about what constitutes a drug candidate; they assert (without references) that it is "well known" that oligonucleotides are poor choices as drugs, and that the "real power of combinatorial chemistry lies in the ability to make libraries of related heterocyclic compounds. . . for screening or lead optimization." This could be seen as an argument that ignores purines and pyrimidines or, conversely, favors continued investment in boats for rapid trans-Atlantic travel. This disagreement will be sorted out in the clinic—aptamers work in many preclinical disease models and we are encouraged, but the need for new drugs is so large that we hope all kinds of combinatorial chemistry (and other screening methodologies) lead to useful compounds.

We disagree strongly with Harris/Buckler regarding the minor point of our article; in some settings, very difficult biology (which translates into very slow, expensive target identification and validation so that drug discovery can proceed) would be helped (or complemented) by inverting the drug-discovery paradigm so that successful drug candidates precede target identification and validation.

If we found an aptamer that crossed the blood brain barrier by "functional SELEX" in vivo and used the aptamer (as in affinity chromatography) to purify and sequence the previously unknown endothelial receptor that afforded that activity, would Harris/Buckler concede that they at least understand what we meant by an inverted paradigm and that something useful (and rational) had been done? The genomic alternative to such an effort might be to identify every receptor present in the neural-specific (tight junctioned) endothelial cells that comprise the blood brain barrier and find compounds (somehow, and slowly) that use those receptors to achieve directional trans-cytosis. The tone of our suggestion was to wonder with readers if scientific knowledge can be obtained with more than one paradigm, and to wonder as well if drug candidates can be found by functional combinatorial chemistry searches.

We like the genomics effort—we praised the endeavor and called it "heroic." One of us (LG) has requested that his gravestone be marked with the unintended praise from the Harris/Buckler letter, "His intellect was revealing in its naiveté." We need more wonder and less certainty in science, including the science of genomics. ///