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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. ///