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LETTERS

Database Contamination

The article "Genome shortcut leads to problems" by Christopher Anderson (News & Comment, 19 Mar., p. 1684) revealed the troubling and potentially widespread problem of contamination of human libraries with nonhuman DNA. Charles Auffray, the director of the Généthon complementary DNA (cDNA) sequencing program, is quoted as saying that yeast contamination was observed in a cDNA clone library purchased from Clontech Laboratories, Inc., of Palo Alto, California. We have also detected the presence of yeast genomic clones in "human liver" cDNA libraries purchased from Clontech. When contacted, Clontech told us that during the preparation of many of their libraries, cDNA was co-precipitated with a yeast transfer RNA (tRNA) preparation before cloning. We hypothesize that the yeast tRNA sample was contaminated by yeast genomic sequences, which were then cloned along with the human cDNA into these libraries. Three independently prepared libraries were sent to us by Clontech, and all were found to be contaminated by yeast sequences.

We initially contacted Clontech with our findings in March 1992, after we observed that supposedly human cDNA clones screened from their library by polymerase chain reaction (PCR) and sequenced were, in fact, yeast sequences. The discovery was fortuitous in that we had only just previously determined the yeast DNA sequence for the same locus we were studying in humans. The Clontech library was unambiguously identified as the source of the incorrect "human" clones. We then screened aliquots of this library, as well as two others by PCR, using a pair of yeast sequence–specific oligonucleotides; all were shown to be yeast-contaminated. Human DNA repeatedly failed to amplify with this primer pair.

We discussed our data in detail with Ted Hung, head of quality control at Clontech, and were told that other researchers were reporting problems with other Clontech libraries. We urged Clontech to make all purchasers aware of the potential problem.

We suggest that all clones isolated from libraries obtained from Clontech, especially those prepared with yeast tRNA, be reexamined to determine whether they are clearly derived from the appropriate species. It is essential that the dissemination of incorrect data be controlled so that additional time and effort will not be wasted.

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We recently developed a genetic selection to recover guanosine 5′-phosphate (guanylic acid) (GMP) synthetase genes or cyclic GMP phosphodiesterase genes by complementation of the *gua*A mutation of *Escherichia coli*. When we used a lambda gt11 library carrying cDNA from *Dictyostelium discoideum* to lysogenize a *gua*A strain of *E. coli*, we recovered both GMP synthetase and cyclic nucleotide phosphodiesterase cDNAs. These cDNAs were from *Dictyostelium*. When we tried to use mammalian lambda gt11 libraries (all from Clontech), we recovered GMP synthetase genes that we believe were from an unknown bacterial species. Southern blots of human DNA showed that none of these GMP synthetase genes was from humans. They had the *gua*BA operon structure of the *E. coli* gene; that is, they were in tandem with an inosine monophosphate dehydrogenase gene. The closest relative in the database was *Bacillus subtilis*, with 60% homology. All of these GMP synthetases had identical restriction maps—one from a rat library, one from a cow library, and five from separate human cDNA libraries. We recovered one phosphodiesterase cDNA, but that wasn't human either: It had the kinetic properties of the bacterial phosphodiesterases and did not hybridize to Southern blots of human DNA. We have concluded that it is not just the CCRF-CEM library used by the Généthon workers that is misbegotten.

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The article "Genome databases worry about yeast (and other) infections" by Christopher Anderson (News & Comment, 19 Mar., p. 1685) raises questions about the reliability of commercial cDNA

libraries. As a leading supplier of these tools, we would like to offer a possible explanation for the reported contamination of the CCRF-CEM cDNA used by the Généthon group mentioned in the article.

Since the initial complaint was reported to us, we have discontinued the sale of this library. We have deduced that the yeast sequences might have been introduced through a low-level contamination of yeast genomic DNA in yeast tRNA (purchased from a respected supplier of research-grade biochemicals) that was used as a co-precipitant of cDNA during cDNA synthesis. Until recently, this method was a common, generally accepted step in cDNA synthesis. It does not affect the quality or functionality of the library when it is used for the purpose for which it was intended (screening with a specific DNA probe). Ambiguity may arise when screening is done with a probe of significant homology to yeast sequences. Unfortunately, we had not anticipated early on that our libraries would be used for massive direct-sequencing purposes, as was done by the Généthon group. Nevertheless, as of November 1992, we stopped using tRNA in the preparation of our libraries.

To further understand the implications of the reported contamination, we also screened 20 libraries, which had been constructed using tRNA, with yeast-specific PCR primers. Eighteen (90%) produced faint positive bands, suggesting a frequency estimated to be less than 0.5%. Probing the same libraries with a 2-kilobase human β-actin cDNA probe revealed 0.15 to 0.9% positive signals, suggesting a normal representation of β-actin sequences. The same 2-kilobase β-actin probe did not produce positive signals when it was used to probe a yeast genomic library.

We agree with the major thrust of Anderson's article—that closer monitoring of the veracity of published sequences is critical. And while we sincerely regret the unfortunate experience of Généthon, we believe the extent of the contamination may not be as great as we initially thought and may represent an extreme case. The libraries we have studied thus far indicate that specific clones can be isolated if specific probes are used. This is further supported by the hundreds of genes isolated and published with Clontech libraries. As preventive measures, in addition to discontinuing the use of tRNA during library construction, we have implemented additional quality control parameters to estimate sequence representation of β-actin sequences in all libraries. We are also developing more rigorous procedures with which to eliminate incidental contamination.

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Sequencing the Human Genome

The article "NIH to appeal patent decision" by Christopher Anderson (News & Comment, 15 Jan., p. 302) incorrectly quotes me as saying that Incyte Pharmaceuticals "will have sequenced the entire human cDNA [complementary DNA] library of 50,000 to 100,000 gene sequences by 1995." We do indeed project that most human genes will be identified by 1995, but not by Incyte alone, as was stated in the article. Rather, we predict such a short time frame on the basis of the efforts of numerous independent groups, both in industry and academia, who, like Incyte, are rapidly expanding their large-scale cDNA sequencing capabilities.