CORRESPONDENCE/

Vaccine Crosstalk

To the editor:

The July 1992 feature "Biotech Vaccines' Problematic Promise" (Stephen M. Edgington, p. 763-766) contained two errors of omission and one error of inclusion of outdated information regarding the status of therapeutic vaccine development at IDEC Pharmaceuticals Corporation.

Our HIV therapeutic vaccine is further along in development than your story indicated. In February 1992, IDEC Pharmaceuticals 3C9, an anti-idiotypic monoclonal antibody, became the first product of its kind in the U.S. to enter phase I clinical trials against HIV infection. IDEC Pharmaceuticals designed 3C9 as a surrogate antigen to trigger the patient's immune system to produce antibodies to the CD4 binding site on HIV, and thereby neutralize the ability of multiple strains of HIV to bind and enter CD4+ cells. By targeting a structurally conserved region of the virus, we hope to overcome the clinical problems associated with rapid mutation of HIV.

Our two candidates for treatment of malignant melanoma were omitted from the chart entirely. Over 100 patients at seven research centers in the U.S. have been treated with our I-Mel-1 or I-Mel-2 anti-idiotypic vaccines in phase II/III clinical trials. At a recent NATO Advanced Studies conference in Greece, we reported that in the serum of the subset of patients we have analyzed so far, both I-Mel-1 and I-Mel-2 monoclonal antibodies stimulate the production of anti-melanoma antibodies in a significant majority of the patients tested.

IDEC Pharmaceuticals' approach to "biotech vaccines" differs somewhat from most other products listed in your table. Rather than using recombinant antigens, we are developing immunologically active monoclonal antibodies for therapeutic applications. Potentially, they offer greater specificity of action, longer therapeutic effect and lower toxicity than is typical of existing therapies.

Richard W. Krawiec
Director, Investor Relations
& Corporate Communications
IDEC Pharmaceuticals
La Jolla, CA 92037

P.S.—I spoke with Tom Cooper who prepared the data at *Bioindex*. I will provide him with updates of our activities, so that his database remains current.

To the editor:

Stephen Edgington's article, "Biotech Vaccines' Problematic Promise" [*Bio/Technology* **10**:766 (1992)] was generally informative, but his discussion of FDA's regulation of vaccines was inaccurate and confusing.

Edgington is muddled on what applications must be submitted to FDA for various products. He says that for vaccines "instead of filing a single investigational new drug application (IND), as with therapeutics, [FDA's Center for Biologics Evaluation and Research] requires two application filings: a product license application (PLA), similar to an IND, and an establishment license application (ELA), a manufacturing license for the vaccine." Actually, whether a product is a "therapeutic" does not dictate where it is regulated or its regulatory requirements. More significant from a regulatory standpoint is whether a product is a "drug" or a "biological" product [see, e.g., H.I. Miller, *Bio/Technology* **6**:1385 (1988)].

Sponsors of investigations on new drugs *or* biologicals (or new uses of approved drugs or biologicals) must file an IND application, which must include information on the product's composition, manufacturing and controls data, animals test results, training and experience of the investigators, and a plan for the clinical investigation. Data generated in successful clinical trials of a *drug* become the substance of a New Drug Application (NDA) to FDA for marketing approval. Among other required information, the NDA must contain a description and analysis of data and other information that bears on the drug's safety and effectiveness.

A biological product (biologic) is "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of diseases or injuries of man. . . ." During the IND phase, FDA applies the same regulations to biologics as to drugs. But for marketing approval of a *biologic*, both the product and its manufacturing facility require licenses. The manufacturer submits a Product License Application (PLA) for the product and an Establishment License Application (ELA) for the facility. Each must meet standards designed to ensure the product's safety, purity, potency, and efficacy. FDA monitors each lot of licensed product released.

Edgington asserts that "unlike therapeutic drug-makers, vaccine-makers fall under the jurisdiction of the Center for Biologics Evaluation and Research" (CBER). In fact, well over 90% of the more than 1100 INDs submitted to FDA for new biotechnology-derived therapeutic products reside in CBER *because the products are biologics*. These important products include the interferons, tPA, colony stimulating factors, monoclonal antibodies for therapy, clotting factors, and so forth.

Edgington notes that, "while purity and potency are quantifiable, safety is the hinge on which the door of acceptance or rejection swings." Safety is also quantifiable, and the hundreds of thousands of pages of safety data submitted to FDA and its ordering by statisticians is testimony to that. Also, as enumerated above, the requirements for marketing approval include assurance of purity, potency, and efficacy, as well as safety; and approval "hinges" on all of these criteria. Determinations by FDA reviewers of these risk/benefit balances are seldom easy, but they are the FDA's everyday responsibility.

The nuances of FDA's regulatory procedures and requirements may sometimes be elusive, but our individual centers and the Office of Biotechnology are always available to re-

spond to specific questions and to attempt to demystify the process generally. The interests of FDA, consumers, and industry are all best served by regulation that is transparent and well understood.

Henry I. Miller
Director
Office of Biotechnology
Food and Drug
Administration
Bethesda, MD 20785

We thank Drs. Krawiec and Miller for their clarifications—the need for which only underscores the problems vaccine development present. While we thank Miller for his charity—the misconstruction of IND and PLA requirements is rather more than a nuance—we must sympathize with neophytes seeking FDA guidance for the first time: a dozen telephone calls logged to FDA's individual centers and the Office of Biotechnology failed to elicit any substantive help on vaccine regulation—certainly nothing as concise as the one Miller offers here.—The Editors

INFORMATION, PLEASE

To the editor:

In his recent report (*Bio/Technology* **10**:752, "What form for Eurobioinformatics?") John Hodgson offers his view of the politics associated with the efforts to design and implement the European Bioinformatics Institute (EBI). While political news may be fun to read, whether it's accurate or not, Hodgson misses the essential point of why the EBI must exist and very soon. That is to ensure European access to, influence on, and expertise for making the best use of the biological information critical to both basic research efforts and the biotechnology industry.

The EMBL Data Library has for over a decade creditably collected and delivered a variety of sequence and related biological information, with much of its effort focused on scientific annotation and data processing and distribution. Continuing this traditional role will certainly require increased funding, but this alone will not ensure that biologists have access to the new forms of information they will need to solve tomorrow's research and biotechnology problems. This will only be possible if the EBI and its collaborators invest in applying the latest computer and informatics technology to managing biological information and in keeping pace with biological research advances. The technology and the science are changing too rapidly to imagine that yesterday's solutions will be viable for long. The information of the near future will be remarkably rich and diverse (not simply text, not simply sequence or map location, but integrated images, structures and function), geographically distributed (available over the international networks) and maintained by numerous independent researchers. There is no one solution for making this information maximally useful except the continuing process of innovation in support of service. Such service and innovation require stable long-term support.

The EMBL Data Library's current funding and facilities do not permit this investment to any significant degree. This is also true for many other bioinformatics resources around the world, and has left some of these moldering away in dusty corners with antiquated solutions to irrelevant problems. Our proposed EBI will continue with the current tasks of the Data Library including its international collaboration (not competition) with the NCBI and others, especially scientists in European academe and industry, but it would be irresponsible of us not to plan and invest for the future. We believe that the EMBL Council and the EC recognise the importance of ensuring the future of the Data Library and will find suitable funding despite economic constraints. However, we have never suggested that the EBI will cost an order of magnitude more than the current Data Library, and we have always planned to seek support from a variety of sources including the EC, EMBL and industry. This will also ensure that all constituencies of the EBI, including users of its services, have a voice in its governance.

Howard Bilofsky
Executive Planning Officer
European Bioinformatics Institute EMBL
Heidelberg, Germany

A European Bioinformatics Institute remains one—but at this stage only one of several—options for European bioinformatics. Ultimately, the community at large must weigh the scientific arguments for and against all of these options though open discussion in public fora—including Bio/Technology.*—The Editors*

DNA Fingerprinting: MAAPing out a RAPD Redefinition?

To the editor:

The advent of a novel strategy for DNA fingerprinting that uses a single oligonucleotide to prime arbitrary segments of a DNA template to produce a characteristic set of amplified fragments promises to be of immense value in the analysis of genetic relationships.[1] The idea was conceived and developed by several laboratories,[2-4] each using markedly different amplification and DNA separation procedures, as well as primers of different length. Fingerprint complexity varies from very simple, and thus ideal for genomic mapping,[2] to highly complex and more suitable for fingerprinting.[4] However, with this novel strategy came different and sometimes incorrect terminologies. The terms Random Amplified Polymorphic DNA (RAPD)[2] and Amplification Fragment Length Polymorphism (AFLP)[4] are used to describe polymorphisms, while Arbitrarily Primed Polymerase Chain Reaction (AP-PCR)[3] and DNA amplification fingerprinting (DAF)[4] describe the actual strategy. AP-PCR conveys a closer description of the amplification strategy, however the use of a single primer to target both DNA strands differs notably from the PCR, in which two primers independently target each DNA strand in a reaction that strives for specificity. What then is the correct term to portray this mapping-fingerprinting procedure? We are all tired of remembering the myriad acronyms that describe the many emerging approaches in molecular biology. If we are to tolerate one more, let us find a suitably correct term, one that encompasses each variation of the overall strategy. We suggest the term Multiple Arbitrary Amplicon Profiling (MAAP) to describe its underlying characteristics: the multiple, arbitrary nature of targeted sites and the amplification of a range of characteristic DNA products. Since MAAP can be used to place markers in a genetic map the acronym may prove appropriate. While proponents of each terminology may resist a new acronym, it is nevertheless important to reach consensus. Because of the RAPD expansion of this new and exciting field we should not delay a decision. *Tous pour un, un pour tous!*

Gustavo Caetano-Anollés
Brant J. Bassam
Peter M.Gresshoff
Plant Molecular GeneticsInstitute for Agriculture
& Center for Legume Research
University of Tennessee
Knoxville, TN 27901-1071

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