

IN brief

Cuba's first GM corn

Cuba will be planting its first genetically modified (GM) corn to help reduce its dependence on costly food imports. The Cuban Center for Genetic Engineering and Biotechnology (CIGB) of Havana will begin the experimental plantation of 125 acres with the GM corn, provisionally called FR-Bt1. This corn is currently undergoing regulatory approval for its environmental release. "Cuban rules are very strict... but in Cuba there is a political will for employing the technology," explains Carlos Borroto, deputy director of the state-run center, and head of the Cuban National Program of Agricultural Biotechnology. The FR-Bt1, whose technical details cannot be revealed due to confidentiality clauses in the registration process, is aimed at animal feed and will be used exclusively in Cuba. The GM crop is engineered to resist the country's main pest: the lepidopteron *Spodoptera frugiperda*. The FR-Bt1 corn was developed by a large CIGB team, led by Camilo Ayra, in collaboration with other research bodies. The entire project was financed with public funds from the Cuban Council of State. "Because the corn has shown an elevated level of multiplication, some 2.5 acres could produce enough seeds to plant 300 acres," says Borroto. Although the use of GM organisms is debated in Cuba, public perception is mostly positive because these developments do not seek commercial gain but the nation's food sufficiency. The outcome of these field trials is expected for April 2009. *—Veronica Guerrero*

EU pushes advanced therapies

This month, the EU Committee for Advanced Therapies (CAT) will be holding its first workshop to discuss the implementation of a new legislation designed to harmonize gene therapies, cell therapies and tissue-engineered products within Europe. The lack of EU-wide regulatory frameworks for such novel therapies has, in the past, hampered the biotech industry's growth and hindered patient access. The recently passed EU Advanced Therapies Regulation lays down rules on the authorization, supervision and pharmacovigilance of newly emerging therapies. The committee, which is responsible for preparing draft opinions on quality, safety and efficacy of advanced therapies for final approval by the Committee for Medicinal Products for Human Use (CHMP), is part of the European Medicines Agency (EMA). It includes representatives from CHMP, member states, clinicians and patient organizations. The regulation outlines a centralized marketing authorization procedure and special incentives for small and medium-sized enterprises (SMEs). Christiane Abouzeid, of the BioIndustry Association, believes that the CAT will help small companies by providing expert advice on complex products. An industry spokesperson notes that incentives for companies and investors within the new Advanced Therapies Regulation will more than offset any short term "pain" while procedures are set up. *—Susan Aldridge*

FDA holds court on *post hoc* data linking KRAS status to drug response

In mid-December, Amgen of Thousand Oaks, California, and its competitor ImClone Systems of New York jointly went in front of the US Food and Drug Administration (FDA) Oncologic Drug Advisory Committee (ODAC) to request permission to shrink the market for their products on the basis of genetic stratification of their target patient populations. Both argued, on the basis of retrospective analyses correlating mutation status with therapeutic response, that their respective anti-epidermal growth factor receptor (EGFR) monoclonal antibodies Vectibix (panitumumab) and Erbitux

(cetuximab) for advanced colorectal cancer should be relabeled for use in only the 60% of individuals whose tumors harbor the wild-type KRAS gene. While the FDA continues to gather opinions and debate internally its criteria for biomarker validation, thus far the agency continues to be reluctant to consider retrospective data, even if such data indicate that a group of patients could be spared futile therapy.

Post hoc re-evaluation of clinical data runs counter to conventional statistical practice at the FDA. According to the agency's standard line of thinking, biomarker and therapeutic

should be developed in parallel and end-points designed prospectively in order for the validity of a hypothesis (and a related null hypothesis) to be tested. For its part, the FDA acknowledges that the science of drug development tied to prognostic indicators is moving at break-neck speed and that new developments may provide reasons for re-evaluating its stance—for example, in situations where patients could be spared futile treatment on the basis



ImClone and Amgen were hoping to include label warnings about KRAS mutations on their products to assist physicians in making treatment decisions for their patients.

SELECTED research collaborations

Partner 1	Partner 2	\$ (millions)
Archemix (Cambridge, Massachusetts)	GlaxoSmithKline (GSK, London)	1,420
Dynavax (Berkeley, California)	GlaxoSmithKline (London)	810
Apitope (Bristol, UK)	Merck Serono (Geneva)	€154
BRAIN (Zwingenberg, Germany)	Genencor/Danisco (Palo Alto, California)	*

*Terms not disclosed.

© 2009 Nature America, Inc. All rights reserved.



of biomarkers identified after a clinical trial has begun or even after a product has been approved for marketing. As a result, the FDA is gathering information on how to assess retrospective biomarker usefulness, and the members of the ODAC panel seemed to be using the confab with Amgen and ImClone scientists as a sounding board to air their questions.

The FDA panel was upfront with its concerns and cited problems intrinsic to retrospective studies. The greatest angst was over “re-analysis of failed clinical trials” in search of alleged efficacy in subsets of biomarker-patient groups that may be undertaken without consideration for missing data and questionable assay techniques. This was a clear warning shot intended to discourage drug developers from rummaging through their discarded and well-worn products with the idea of manipulating data to make a drug fit some selectively back-tested and redistilled class of patient, biomarker and disease. “We are in agreement with that,” says Hagop Youssoufian, senior vice president of clinical research and development at ImClone Systems, now a wholly owned subsidiary of Eli Lilly of Indianapolis, Indiana. “But that was never the purpose of the *KRAS* analysis anyway,” he says. Both Erbitux and Vectibix won FDA approval as second-line therapies in the US without regard to biomarker status.

The ODAC panel didn't spend much time contesting the conclusions about *KRAS* status and drug response put forward by Amgen and ImClone speakers; instead, it acted more as devil's advocate. By nearly everyone's account, the all-day meeting offered a vigorous debate that was “constructive” and even friendly. “We viewed it as a collaborative effort to really try to move the field forward,” says David Reese, who has been Amgen's

Box 1 FDA considerations for retrospective drug-biomarker analysis

The FDA has circulated six items that would likely be a minimum starting point for them to assess a retrospective analysis from a clinical trial:

- The trial must be adequate, well-conducted and well-controlled;
- The sample size must be sufficiently large to be likely to ensure random allocation to each of the study arms for factors (such as *KRAS* status) that were not used as stratification variables for randomization;
- Tumor tissue must be obtained in $\geq 95\%$ of the registered and randomized study subjects and an evaluable result (presence of wild-type or mutant *KRAS*) must be available for $\geq 90\%$ of the registered and randomized study subjects;
- Before analysis, the FDA must have reviewed the assay methodology and determined that it has acceptable analytical performance characteristics (for example, sensitivity, specificity, accuracy, precision) under the proposed conditions for clinical use;
- Genetic analysis must be performed according to the qualified assay method by individuals who are masked to treatment assignment and clinical outcome results;
- Before analysis of clinical outcomes based on the genetic testing, agreement with the FDA must be reached on the analytical plan for hypothesis testing for proposed labeling and promotional claims.

Source: Adapted from FDA's Oncologic Drugs Advisory Committee meeting briefing document, 16 December 2008

global development leader for the Vectibix program. “We shared our data as an example of how these things actually transpire in the real world to help inform their thinking.” Amgen's Vectibix won US approval in September 2006, and ImClone's Erbitux got its US approval in February 2004. But during the period between 2005 and 2007, new data were emerging (Table 1) that demonstrated *KRAS* status to be an important indicator with regard to the use of either Vectibix or Erbitux in colorectal cancers.

Meanwhile, European Union (EU) approval for Vectibix came at the end of 2007 complete with a label restriction to the *KRAS*-wild-type tumor subgroup. And Erbitux received a similar label restriction based on *KRAS*

status more recently. In the EU, where public health systems prevail, product approval following European Medicines Agency (EMA) recommendations does not guarantee that a patient will receive a drug. An insurer can veto a product's use if there is no compelling evidence of efficacy in a given situation, which makes off-label use close to impossible for most patients. Therefore, prognostic biomarkers are particularly valued because they often provide a more compelling risk/benefit ratio for individual patients.

In theory, for Amgen and ImClone's case, performing a new clinical trial with a *KRAS* status hypothesis and new endpoints would solve the FDA's quandary, but the reality is that such an idea just won't fly now. “With the

Details

Archemix and GSK have partnered to develop new aptamer therapeutics against interleukin-23 and six undisclosed targets with relevance to inflammatory disease. Archemix will receive \$27.5 million upfront and is eligible to receive up to \$200 million in development, regulatory and sales milestones for each of the seven aptamer products. The biotech would also receive tiered royalties up to lower double-digits.

The two companies plan to develop and market inhibitors of endosomal toll-like receptors (TLRs) to treat autoimmune and inflammatory diseases. GSK will pay \$10 million upfront for an exclusive option to license four programs. The deal includes Dynavax's DV1079, a bifunctional TLR7 and TLR9 inhibitor about to start phase 1 testing. The biotech is entitled to about \$200 million in milestone fees for each program.

The companies have signed a deal to collaborate on the development and commercialization of Apitope's peptide therapeutic for multiple sclerosis, which has just completed a preliminary clinical study. Apitope will receive up to €154 million in upfront, development and sales milestone payments. Apitope's peptide ATX-MS-1467 is designed to induce immunological tolerance to autoantigens involved in multiple sclerosis.

BRAIN has joined forces with Genencor to use metagenomics to develop enzymes for the production of products to replace petrochemicals in biofuels, plastics, rubber, adhesives and cosmetics. Genencor will use its capabilities in metabolic pathway engineering and biomanufacturing of industrial bioproducts. BRAIN will provide Genencor access to its technologies, in particular its metagenome resources of some 150 million genes of yet uncultured microorganisms. Enzymes and biosynthetic pathways of interest will be genetically engineered in microbial production strains for the production of biochemicals.

Table 1 KRAS status and response to EGFR antibodies in colorectal cancer

Publication	Treatment (panitumumab or cetuximab)	Number of subjects (wild type; mutant)	Objective response, n (%)	
			Mutant	Wild type
<i>Lancet Oncol.</i> 6 , 279–286 (2005)	Panitumumab or cetuximab or cetuximab + chemotherapy	31 (21; 10)	2 (20)	8 (38)
<i>Cancer Res.</i> 67 , 2643–2648 (2007)	Panitumumab or cetuximab or cetuximab + chemotherapy	48 (32; 16)	1 (6)	10 (31)
<i>J. Clin. Oncol.</i> 25 , 4132 (2007)	Cetuximab ± chemotherapy	37 (20; 17)	0 (0)	17 (46)
<i>J. Clin. Oncol.</i> 2 , 4021 (2007)	Cetuximab ± chemotherapy	81 (49; 32)	2 (6.3)	13 (26.5)
<i>J. Clin. Oncol.</i> 25 , 3230–3237 (2007)	Cetuximab	80 (50; 30)	0 (0)	5 (10)
<i>AACR Meeting Abstracts 2007</i> , 5671 (2007)	Cetuximab ± chemotherapy	78 (49; 27)	0 (0)	24 (49)

overwhelming consistency of data we have for Erbitux and Vectibix, no one has any inclination to administer these drugs to patients with KRAS-mutant tumors,” says ImClone’s Youssoufian. “You would be randomizing and subjecting patients to a drug that could, at minimum, be neutral, if not associated with adverse effects.”

The data are out for oncologists to see, and nearly every clinician is ostensibly aware that KRAS mutant–harboring tumors are no longer candidates for anti-EGFR products. In addition, the National Comprehensive Cancer Network’s guidelines make a strong recommendation to reserve Erbitux and Vectibix for tumors with the wild-type KRAS. So the message is sinking in. “The problem for us as a company,” says Youssoufian, “is that we cannot proactively disseminate that message because it’s simply not in our label.” And Amgen’s Reese says, “We think it’s the correct science, and we have an obligation to communicate the appropriate information to patients and physicians, and the mechanism for us to do that is the label. That formed the basis of our proposal.”

If Amgen and ImClone were lingering under any illusion that the discussion might lead ODAC to recommend that the agency include KRAS status in their drug labels, they were proven wrong. The panel clearly didn’t feel inclined to comment—at least for now. “Really, everyone has already implemented KRAS testing, so what is the big deal if the agency makes a decision right away or not?” says senior biotech analyst Aaron Reames of Wachovia Securities. “The issue is not with the anti-EGFR monoclonal antibodies in this case but rather the precedent that this decision will set.”

Biostatistician Richard Simon of the National Cancer Institute of Bethesda, Maryland, favors the Amgen-ImClone proposal to tie KRAS status to anti-EGFR therapy. But he understands the suspicion engendered

by retrospective studies. “When I’ve given talks, I have gotten questions from people at the FDA who express concern about companies reanalyzing the same clinical trial with regard to multiple biomarkers,” he says. “The kind of retrospective studies that we’re used to seeing are not very reliable because they don’t have a single biomarker hypothesis. There is skepticism because we’ve seen so much garbage come from *post hoc* data dredging.”

The FDA presented Amgen and ImClone with six considerations for a valid retrospective analysis (see Box 1). One of the more important issues was the type of KRAS assay used (*Nat. Biotechnol.* **26**, 839–840, 2008). Both companies are largely in compliance with the points in question, but if or exactly when their labels will be revised is anybody’s guess. An Amgen spokesperson will say only that the company remains in “productive discussions” with the FDA.

The potential financial consequences of a label change for Amgen and ImClone are also unclear. Senior biotech analyst Eric Schmidt of Cowen does not think limiting Vectibix and Erbitux will have a substantial impact on the companies’ profits. Of the estimated 40% colorectal cancer patients with KRAS-mutant tumors, he says: “They were likely receiving shorter courses of therapy due to their unresponsiveness.” He expects no more than a 10–30% decline in product revenues; however, he envisions a potential offset resulting from more frequent testing for KRAS status. “Awareness that a patient is KRAS wild type could drive adoption of Erbitux and Vectibix in more second-line patients,” he says. From Schmidt’s point of view, there’s no significant dollar loss or gain resulting from limiting use of the drugs. “I think these companies simply believe this is the right thing to do, and that they are facilitating better medicine, better utilization of healthcare dollars and better citizenship,” he says.

George S. Mack Columbia, South Carolina