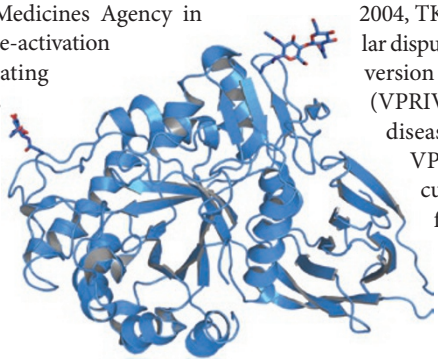
Shire's replacement enzymes validate gene activation

Genzyme's manufacturing strife and the urgent search for alternatives to meet patients' needs have propelled Shire and its gene-activation technology to the fore. When Genzyme's Allston Landing facility was shut down in 2009 after the discovery of viral contamination, the US Food and Drug Administration (FDA) requested Chineham, UK–based Shire's help in maintaining enzyme supplies for Fabry and Gaucher patients, prompting the company to accelerate its manufacturing timeline for VPRIV (velaglucerase alfa, glucocerebrosidase) by 18 months. The reward was an accelerated approval. VPRIV received the FDA's nod in February 2010, and that of the European Medicines Agency in August 2010. Shire's gene-activation technology for generating human proteins has thus emerged as a powerful rival to recombinant technologies. After 20 years in which its potential was obscured by corporate posturing and patent wars, the technology now forms the basis of two of Shire's enzyme replacement therapies: Replagal (agalsidase alfa) for treating Fabry disease, approved in Europe and currently under fast track designation in the United States, and VPRIV for Gaucher disease.



Shire generated VIPRIV velaglucerase alfa, structure shown here, not by recombination but by targeted activation of an endogenous gene in a human cell line.

Gene-activation technology involves introducing a DNA promoter upstream of an endogenous gene in a human cell line. This must be done at a precise location, chosen through knowing the sequence of the gene to be activated. There is an appealing simplicity to the idea of activating an existing gene, rather than the recombinant approach of cloning the gene and introducing it into a mammalian or bacterial cell line. Shire and its antecedents were not alone in pursuing this technology, raising the question of why gene activation has taken so long to translate through to the market.

The answer lies in a fiercely defended intellectual property estate in biotech—Thousand Oaks, California–based Amgen's erythropoietin (EPO) patents—plus a couple of minor skirmishes with Genzyme of Cambridge, Massachusetts, over enzymes for treating Gaucher and Fabry diseases, and lastly, a US Securities and Exchange Commission (SEC) investigation.

Amgen used a monolith of patent rights on its method for manufacturing EPO, to stop Shire Genetic Therapies' forerunner, Transkaryotic Therapies (TKT; formerly of Cambridge, Massachusetts), from producing EPO. TKT threw down the gauntlet to Amgen in the prospectus for its initial public offering in October 1996, stating that the first approval for its gene-activation technology would be Dynepo (epoetin delta), a version of EPO, which it was then developing in collaboration with Hoechst Marion Roussel (later Aventis Pharma) of Kansas City, Missouri.

This prompted Amgen to file patent suits against TKT. Although that dispute wound its way around the US and UK courts from 1997 to 2004, TKT found itself in a similar dispute over its gene-activated version of glucocerebrosidase (VPRIV) for treating Gaucher disease. Genzyme claimed VPRIV infringed its cell culture process for manufacturing its marketed treatment Cerezyme (imiglucerase) for the same disease.

At the same time, TKT was in a head-to-head race with Genzyme for the coveted prize of US Orphan Drug status—and seven years' marketing exclusivity—in Fabry disease. In the event, in January 2004, Genzyme's Fabrazyme (agalsidase beta) received the nod from the FDA, whereas TKT was told that although its drug was approved in 27 other countries, the file for Replagal, its Fabry disease treatment, did not demonstrate efficacy. Just before the FDA reached this conclusion, Richard Selden CEO, who founded TKT in 1988, became the subject of an SEC investigation on suspicions that he withheld information about the FDA's negative views on Replagal from shareholders, while selling shares of his own.

In 2003, Selden resigned from the company and was subsequently found guilty by the SEC in July 2008 and fined $1.2 million. As the patent disputes trundled on, the new CEO Michael Astrue worked to restore TKT's credibility. Finally, in October 2004, in the third hearing of the case, the UK House of Lords ruled in favor of TKT in the dispute with Amgen.

Little matter that a few days earlier a US federal judge had upheld four of Amgen's EPO claims, ruling that the company had been infringed by TKT, because the UK ruling

IN brief

Pharmacogenomics row

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Amgen's Vectibix scrutinized.

A new US government–sponsored report on three pharmacogenetic tests for targeted cancer treatments has confirmed the usefulness of *KRAS* testing but raised doubts about two other widely adopted tests. The Agency for HealthCare Research and Quality (AHCRQ) commissioned the report at the request of the Centers for Medicare and Medicaid Services (CMS) to help set clinical guidelines and reimbursement policies. The report, produced by researchers at the Tufts Evidence-Based Practice Center, Boston, examined published studies linking *KRAS* mutations and the ability to predict responses to two colorectal cancer antibody therapies: Erbitux (cetuximab) from Bristol-Myers Squibb and ImClone, and Vectibix (panitumumab) from Amgen. The team also analyzed studies of genetic variants in *CYP2D6* (cytochrome P450) as response predictors to AstraZeneca's breast cancer drug Nolvadex (tamoxifen); and studies of *BCR-ABL1* mutations as response predictors to Novartis's Gleevec (imatinib) and Bristol-Myers Squibb's Tasigna (nilotinib) in leukemia treatments. The report's conclusion affirmed the value of *KRAS* testing in colorectal cancer therapies but found no evidence for consistent associations between *BCR-ABL1* status and response to tyrosine kinase inhibitor treatment or *CYP2D6* polymorphism status and response to Nolvadex. Mark Ratain, director of the Center for Personalized Therapeutics at the University of Chicago and one of the report's official reviewers, expressed outrage at the *CYP2D6* finding. "This [analysis] is a tremendous disservice to taxpayers and patients," he says. "Medco [pharmacy services firm] is testing all their patients and I would never order this drug without a test." Nolvadex is a pro-drug, and "strong laboratory evidence" exists that individuals with certain *CYP2D6* genotypes cannot metabolize it properly, Ratain notes. According to Ratain, the original version of the report did not reference the largest study by far on *CYP2D6* testing (*JAMA* **302**, 1429–1436, 2009) and "lumps bad studies with good ones." The report's conclusions could encourage more widespread use of *KRAS* tests. But Grace Wang from the Centers for Translational and Policy Research on Personalized Medicine at the University of California, San Francisco, says it might make it harder to get reimbursement for *CYP2D6* and *BCR-ABL1* testing. Overall, she notes, "The report really highlights what we don't know" about the benefit and harms of testing. *Malorye Allison*