The origins of new drugs

To the editor:

There is some debate as to the relative contribution of publicly funded research (universities, government research institutes and academic medical centers), biotech companies and pharmaceutical companies to the discovery of new medicines. To gain a clearer understanding of the origin of newly marketed drugs, I have analyzed data from the US Food and Drug Administration (FDA, Rockville, MD, USA), US Securities and Exchange Commission (SEC, Washington, DC) and the US Patent and Trademark Office (PTO, Washington, DC) to determine the origin of most of the new molecular entities (NMEs) and new biological entities (NBEs) approved by the FDA from 1998 to 2003.

To carry out this analysis, I obtained lists of NMEs and NBEs approved each year from 1998 to 2003 from the FDA website (http://www.fda.gov/), which provided each drug's sponsor (that is, the company seeking drug approval that usually owns the drug or holds an exclusive license to the patents covering the drug). In the case of NMEs, the sponsor must identify the patents (if any) describing the chemical compounds that constitute the NMEs (if such compounds are patentable), methods of NME manufacture or uses of the NME. I excluded from the analysis nine NMEs that are imaging agents and one chemical warfare protective paste developed by the US Army. I found patents covering all the other NMEs (some expired but still relevant as to origin) except Vioxx (rofecoxib; 1999), which Merck (Rahway, NJ) has recently withdrawn from the market, and nine other NMEs for which the FDA Orange Book states "no unexpired patents". (SEC documents showed that one of these nine, Valstar (valrubicin; 1998, originated in Dana Farber.) In addition, a few NMEs only have recently filed use or method-of-delivery patents that do not provide clues as to origin. Nevertheless, the patent records combined with SEC documents and occasional internet searches give a fairly good picture of the main loci of early stage and preclinical development in the case of all but 14 of the total 145 NMEs. In the case of NBEs, I reviewed Recombinant Capital's *Signals Magazine* (http://www.signalsmag.com), which periodically publishes analyses of licensing data from its rDNA database (http://www.recap.com/rdna.nsf). I also reviewed 10-K reports filed annually to the SEC by the companies that sought FDA approval for the NBEs. Small and mid-sized biotech companies often mention the existence of in-licenses covering their NBEs that have just received FDA approval, although pharmaceutical companies and large biotechs rarely mention such in-licenses. It is possible that I have not identified the principle origin of some of the NBEs submitted for approval by pharmaceutical companies and large biotechs. The results of the analysis are summarized in **Table 1**.

The data reveal that at least 39% of all (171) drugs (both NMEs and NBEs) approved by the FDA from 1998 to 2003 originated from outside pharmaceutical companies: ~24% came from biotech companies and at least 15% came from public research. Of the drugs that originated from public research, 19% were licensed to pharmaceutical companies and 81% were licensed to biotech companies. In cases when a public research institution's patents had expired, the drug

Table 1 The origin of FDA-approved medicines

Category	Year(s) approved by FDA						
	1998	1999	2000	2001	2002	2003	1998–2003
FDA drug approvals							
Total	34	34	28	26	22	27	171
No. originating from biotech R&D	14	11	9	8	7	13	62
No. based on university invention	4	8	4	3	2	5	26
University inventions licensed directly to pharma company	1	2	2	0	0	0	5
New molecular entities (NMEs)							
Total	29	33	26	21	15	21	145
No. originating from biotech R&D	10	10	7	4	2	7	40
No. based on university invention	4	7	4	1	1	3	20
University inventions licensed directly to pharma company	1	2	2	0	0	0	5
New biological entities (NBEs)							
Total	5	1	2	5	7	6	26
No. originating from biotech R&D	4	1	2	4	5	6	22
No. based on university invention	0	1	0	2	1	2	6

was simply developed by a pharmaceutical or biotechnology company. Thus, biotech companies either discovered or played a major role in developing 36% of all new drugs (NMEs and NBEs).

As expected, biotech companies have dominated the development of NBEs, discovering or playing a key role in the development of 22 (85%) of the 26 new NBEs. Of the 22 biotech NTBs, six (27%) were licensed to pharmaceutical companies, which then applied for FDA marketing approval. Biotech companies themselves applied for marketing approval for the remaining 16. In 4 of these 16 cases, the biotech that applied for marketing approval had in-licensed the NBE from another biotech. At least 6 (27%) of the 22 biotech-developed NBEs were based upon inventions made in public research. There appear to be no cases of a university directly licensing an invention covering an NBE to a pharmaceutical company.

Biotech companies and public research also contributed to a significant but lesser degree to the discovery of new NMEs, at least 45 (31%) of which were discovered outside of pharmaceutical companies. Forty (27%) were discovered or developed in biotech companies, and in most of these cases, a biotech company pursued development all the way to obtaining marketing approval. In the case of 30 of the 40 biotech company-developed NMEs, the biotech company was also the applicant for FDA marketing approval. Nine of these 30 were licensed from one biotech company to another, which subsequently assumed responsibility for obtaining FDA approval. Twenty (14%) of the NMEs are covered by university patents. Five of the drugs of university origin were licensed directly to pharmaceutical companies rather than to biotechs. Fifteen (38%) of the 40 NMEs developed by biotech companies originated in public research institutions.

Others have described the importance of linkages between universities, biotech companies and pharmaceutical companies for the discovery and development of new drugs[1–6]. The analysis described here provides an objective estimate of the contribution in drug discovery not only of biotech companies but also of public research (to the extent that university involvement is reflected in patents covering the new drugs).

In the case of NBEs, the data indicating the contribution of public research or biotech companies to drug discovery are lower-bound estimates because the FDA does not publish information about the patents covering NBEs. Thus, it is difficult to know whether a pharmaceutical company that has received permission to market an NBE might have in-licensed the NBE from a biotech company or public research institution. It is also difficult to know whether a biotech company that has received marketing approval for an NBE might have in-licensed key discoveries from a public research institution, although the SEC filings often provide this information.

In addition, patents reflect only a portion of the total contribution to drug discovery and development. Cockburn[1] has shown that even before university patenting of biomedical discoveries became commonplace, the vast majority of the most therapeutically important drugs approved in the 1960s and 1970s owed their discovery in large part to public research. On the other hand, even though patented discoveries in a university or biotech laboratory may have been important in the discovery or development of a new drug, subsequent R&D in the pharmaceutical or biotech company that ultimately applies for approval also reflects considerable scientific and innovative effort. Thus, these findings do not suggest a diminished contribution of pharmaceutical companies but rather confirm the integrated nature of drug discovery and development and the substantial contributions of biotechnology companies and universities.

Compared with Cockburn's earlier analysis, the data presented here also suggest that a larger proportion of university discoveries directly relevant to drug discovery are now being transferred as formal patent licenses to new small companies. These formal (and presumably exclusive) licenses undoubtedly help biotech companies to obtain private investment and thereby continue drug development. These findings also indicate that biotech companies which are the original discoverers of drugs ultimately approved (whether NMEs or NBEs) more often than not pursue development of these drugs all the way through approval. One interpretation of this finding is that, when a biotech company discovers a drug that turns out to be a winner, it usually manages to obtain resources to pursue development all the way to marketing approval (that is, biotech companies and their investors do a pretty good job of picking and holding onto winners). However, size does matter. Small biotechs are more likely to out-license their winning drugs than large biotechs. Finally, although I show data for each year, clear time trends are not apparent.

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Framing the issues on transgenic forests

To the editor:

Your News Feature in the February issue (*Nat. Biotechnol.* **23**, 165–167, 2005) highlighted rapid advances being made in forest molecular domestication. Counter to Herrera's assertion that "most of the global funding for forest biotech is being funneled to universities," the pursuit of genetic engineering in forest research is principally corporate, shaped by the imperatives of private investment, market forces and government regulatory institutions. Novel forest tree phenotypes are thus created as a means to increase shareholder value of investor companies. And although potential benefits will accrue to shareholders, it is clear that ecological risks of certain transgenic traits engineered into trees are likely to be shared by all. Indeed, as the forest-products companies driving adoption of transgenic technology hold less than 11% of US forest acreage, it is the remaining majority—public landowners and private small woodlot owners—that stands to lose the most.

Herrera indicates in his article that for forest biotech, "investors are virtually nonexistent." Even so, private investment in forest biotechnology is still sufficient to be fueling the creation of novel transgenic phenotypes in trees at a rate that is outstripping public policy deliberation and scientific assessment of environmental concerns specific to trees. For example, trees disperse their seed and pollen over unprecedented distances compared with crops. The sheer scale of gene flow dynamics