National origins of new drugs

To the editor:

Using the same methodology as I described in the May issue (*Nat. Biotechnol.* **23**, 529–530, 2005), I have further analyzed data from the US Food and Drug Administration (FDA, Rockville, MD), US Securities and Exchange Commission (SEC, Washington, DC) and the US Patent and Trademark Office (PTO, Washington, DC) to obtain clues as to where drugs recently approved by the FDA were discovered. Overall, 40% of new drugs originated in either universities or biotech companies. However, this average value hides great variation among countries, as shown in **Table 1**.

My analysis attributes a country of discovery to each of the 170 new molecular entities (NMEs) and new therapeutic biological entities (NBEs) approved by the FDA between 1998 and 2003. In the case of NMEs, this attribution was based upon the history of the discovery and development of each NME reconstructed in so far as possible from the drug approval and patent records. As I emphasized discovery of validated drug candidates, not improvements on existing candidates, I placed greatest emphasis on early drug composition patents covering the class of compounds that eventually became approved drugs. I relied on method of use or method of manufacture patents only in the absence of drug composition patents. My main indicator of discovery location was the domiciles of the inventors listed on the key patents (see **Supplementary Methods** online for more details).

In the absence of such patents, I relied on data available from SEC filings (usually available for small to mid-size biotechs, but not for large or foreign biotechs), and in the absence of SEC data, on the location of the company applying for approval to the FDA or other information I could glean.

Table 1 summarizes the number of new drugs whose discovery I attributed to each of the seven leading countries in terms of drug discovery. Nearly two-thirds of drugs discovered in the United States were discovered in biotech companies, universities or government research institutes, not in established pharmaceutical companies. In the case of NBEs, discovery was heavily concentrated in the United States, almost all of which occurred in biotechs or universities. The pattern in Canada seems similar to the US. In contrast, only a small percentage of approved drugs resulted from discovery in biotech companies in continental Europe. In this respect, the UK appears intermediate between the North American and continental European patterns, reflecting the relative strength of the UK biotech sector compared with continental Europe.

Drug discovery in Japan also occurs almost entirely in established companies and so far there have been no Japanese NBEs. Among the Japanese companies, only R-Tech Ueno (Tokyo), established in 1994, and discoverer of Rescula (unoprostone isopropyl; approved in 2000) would qualify as biotech. A perhaps uniquely Japanese phenomenon is small pharmaceutical operations within non-pharmaceutical companies. Of the 18 new Japanese drugs, three were discovered in food products companies: Evoxac (cevimiline hydrochloride; (in part) Snow Brand, Tokyo); Starlix (nateglinide; Ajinomoto, Tokyo); and Spectracef (cefditoren pivoxil; Meiji Seika, Tokyo), whereas Eloxatin (oxaliplatin) came from a precious metals company, Tanaka Kikinzoku Kogyo (Tokyo). From the licensing behavior of these small pharmaceutical operations (and even some of the small-midsize pharmaceutical companies, such as Kyorin), most license their drugs to large pharmaceutical companies (often overseas companies)

Table 1 New drugs approved by FDA (1998 to 2003) by inventors' domicile and large/small company affiliation.

	NMEs[1]		NBEs[1]		NMEs + NBEs[1]		
Domicile of inventors	Total[2]	Nonpharma[3]	Total[2]	Nonpharma[3]	Total[2]	Nonpharma[3]	Share of 2003 world pharma market[4]
US	58.7 (41%)	32.8 (56%)	22 (85%)	20 (91%)	80.7 (47%)	52.8 (65%)	44.4%
Japan	16.9 (12%)	1.0 (6%)	0	0	16.9 (10%)	1.0 (6%)	12.3%
UK	14.5 (10%)	3.0 (21%)	0	0	14.5 (9%	3.0 (21%)	3.8%
Germany	12.9 (9%)	0.8 (6%)	0	0	12.9 (8%)	0.8 (6%)	6.0%
Switzerland	9.8 (7%)	1.3 (13%)	2 (8%)	0	11.8 (7%)	1.3 (11%)	0.6%
France	7.7 (5%)	1.0 (13%)	1 (4%)	0	8.7 (5%)	1.0 (11%)	5.7%
Canada	4.0 (3%)	2.0 (50%)	0	0	4.0 (2%)	2.0 (50%)	2.1%
Other	17.5 (12%)	5.9 (34%)	1 (4%)	1	18.7 (11%)	6.9 (37%)	25.1%
Unknown	2.0	2.0					
Total	144.0	47.8 (33%)	26	21	170.0	68.8 (40%)	100.0%

[1]Because drugs often share inventors from more than one domicile, drugs per country are not tabulated as integers. Thus, in the simplest case, a drug with inventors from Japan and the US is scored 0.5 for Japan and 0.5 for the United States (see **Supplementary Methods** online). [2]Number in parentheses specifies country's drug output as a percentage of world total for that type of drug. [3]Number in parentheses is specific country's ouput of that type of drug originating outside of pharma as a percentage of that country's total output for that type of drug (university, biotech, government research institute, pharma). [4]Japan Pharmaceutical Manufacturers Association. *Textbook of the Pharmaceutical Industry 2005* (in Japanese) abstracting data from the IMS Midas database and survey of global pharmaceutical markets (available via subscription at www.ims-global.com/products/sales/midas.htm).

before clinical trials are complete (see **Supplementary Table 1** online).

Is it possible that some of the Japanese and European drugs I have attributed to large pharmaceutical companies actually had university co-inventors. US patents do not list the inventors' affiliations. Also, until recently in Japan, Germany and some other European countries, universities did not claim ownership over their inventions. Rather than being patented by the universities, any commercialization would depend upon the university researchers passing their inventions directly to companies. However, according to analysis of the pipelines of Japan's largest pharmaceutical companies and interviews concerning these pipeline drugs, cases of university researchers directly contributing to drug discovery appear to be quite rare[1]. Therefore, at least in the case of Japan, few if any of the approved drugs from pharmaceutical companies are likely to have university co-inventors.

What does **Table 1** have to say about the relative strength of drug discovery capabilities in various countries? From the perspective of sheer numbers of new drugs, clearly the United States is in a dominant position and this dominance depends greatly upon R&D in universities and biotechs. But using each country's share of the global pharmaceutical market as a benchmark gives a more balanced picture. Indeed, the United States and Canada are approximately where they should be. Japan, with 10% of all newly approved drugs, is slightly low compared with its 12% share of the world market. However, this discrepancy vanishes if the analysis is limited only to NMEs. The European countries, particularly the United Kingdom and Switzerland, seem to be doing quite well in relation to market size.

This may give pause to persons who have bemoaned the absence of vibrant biotech companies in Europe and Japan. Granted, the synergistic relationship between universities, biotechs and big pharma is better developed in North America than anywhere else. Even so, these data suggest that, at least in Europe and Japan, and at least with respect to NMEs, in-house research teams in large pharmaceutical companies are discovering drugs at a pace that is competitive with the United States, where biotech companies now dominate drug discovery.

Does this mean that the relationship between R&D in biotech companies and pharmaceutical companies is one of substitution rather than complementation? Perhaps, but not necessarily. Numbers of approved drugs may not be as good a measure of the value as market sales. But using this metric as well, Japan's system of drug discovery based on in-house pharmaceutical research teams does not seem markedly inferior. Among the top selling 200 drugs world-wide in 2002, Japanese origin drugs accounted for 11.3% of sales that year. This represents a significant rise since 1996 when pharmaceuticals of Japanese origin accounted for only 6.1% of the $96.4 billion in worldwide sales of the 200 top selling drugs (data provided by the Japan Pharmaceutical Manufacturers Association, Tokyo). It is also close to Japan's share of the global pharmaceutical market.

More fundamentally, however, share of world pharmaceutical market may not be a good benchmark. After all, the United States' 44% share of that market is substantially higher than its share of, for example, world gross domestic product. It may be that the high US market share in pharmaceuticals is both a symptom and a cause of a healthy environment for pharmaceutical innovation.

Note: Supplementary information is available on the Nature Biotechnology website.

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Cross-border biotech

To the editor:

We read with interest the Feature by Ken Howard Wilan entitled "Chasing biotech, state by state—winners and losers" (*Nat. Biotechnol.* **23**, 175–179, 2005). One theme highlighted in the article is the myopic city- or state-level focus of many biotech initiatives and the paucity of examples of multi-state (or even bi-state) biotech collaborations in the United States. This contrasts with Europe, which has established several cross-border life science clusters (localized concentrations of biotech firms and support services) over the past decade. What factors account for this difference?

One key difference between the United States and Europe is the amount of high-level support for cross-border cooperation. For example, the European Union's (EU) Interreg Community Initiative, adopted in 1990, is intended to prepare European border areas for a community without internal frontiers[1]. The current iteration, Interreg III, which is financed under the European Regional Development Fund, expires at the end of 2006. It aims to strengthen economic and social cohesion by fostering cross-border cooperation (Interreg III A), transnational cooperation (Interreg III B) and interregional cooperation (Interreg III C).

The Interreg Community Initiative has provided impetus to two prominent European multi-national life science clusters, Medicon Valley and BioValley, which formed around regional centers of research excellence. These clusters were formalized in the late 1990s by the formation of dedicated initiatives to support research and commercialization endeavors.

Medicon Valley comprises a concentration of biotech firms and related organizations located in the Metropolitan Copenhagen Region in Denmark and the Scania province in southern Sweden, geographically and politically separated by the Øresund Sound and the Danish/Swedish border. The impetus to formalize a life sciences cluster in Medicon Valley stemmed from a 1993 report revealing that Medicon Valley was home to 60% of Scandinavian pharmaceutical companies and was ranked third in Europe on the basis of number of medical publications by researchers in the region[2].

The Medicon Valley Academy (MVA, Copenhagen) was set up in 1997 as a Swedish/Danish network organization supported by the regional universities and the EU Interreg II program. The aim was to catalyze integration and development and to create regional networks in the life sciences that integrate and pool resources and expertise from academia, industry and public organizations. The MVA has since matured into a member-supported nonprofit networking organization, representing all the relevant university departments, healthcare organizations and most of the biotech and medical companies and related organizations in the region.

Although there are very few reports of positive outcomes from the Medicon Valley initiative as yet, several tangible benefits for research in the area have resulted; for example, the MVA coordinates a PhD and postdoctoral cross-border research program, which is jointly funded by the governments of Sweden and Denmark. A common feature in the program is that the participants act as 'conduits,' connecting regional entities with specialized facilities and expertise on both sides of the national border. The Øresund