

The Importance of New Companies for Drug Discovery and Development: an Analysis of the New Drugs Approved by the FDA 1998-2003¹

Robert Kneller
Research Center for Advanced Science and Technology
University of Tokyo

Preface

This paper analyzes the origins of all the 169 new drugs approved by the US Food and Drug Administration (FDA) from 1998 to 2003. It shows the types of organizations (pharmaceutical companies, biotechnology companies or universities) that are discovering innovative drugs and the countries/regions in which these discoveries are being made. The variations are striking and have implications for public health and the types organizations, business environments and public policies that promote the discovery and commercialization of innovative drugs.

Introduction and summary of methodology

This analysis uses a standard methodology to identify the discoverers of these drugs and the laboratories in which they were working. Using patents covering new molecular entities (NMEs) listed in the FDA Administrative Correspondence or the FDA Orange Book and two other principal, public data sources, I identified the key patents covering most of these drugs, and then the inventors on these patents and their places of work. For the vast majority of inventors, place of invention was determined by scientific papers (usually related to the drug) that they co-authored within 4 years of the patent application date and that stated their place of work. For fewer than 20 percent of inventors, I relied instead on a consistent history of patent applications to indicate that the inventor was employed in a particular laboratory. For each drug I determined a set of key patents, and weighted them according to the extent to which they represent discovery of the key therapeutic compound, or proof of therapeutic concept in a live mammal. (If no key patents ever existed, then I determined a similar weighted set of key scientific articles identifying the researchers most responsible for discovery, proof of therapeutic concept, or for taking the initial steps towards development, and their places of employment.) For each key patent, I weighted the contributions of all inventors equally. Thus I attributed each drug's origin in percentage

1. In order to keep this manuscript to a manageable length, I have omitted much information on methodology and specific drugs, as well as several references and data tables. Such information appears in another paper now being prepared for publication. However, I have kept a few footnotes mentioning specific drugs and one appendix case study for illustrative purposes.

fashion according to country, and, separately, according to type of discovering organization. The latter I categorized as:

- Pharma: i.e., in-house laboratories of a company with more than 500 employees established no later than 1975,
- Biotech: a company established after 1975, or a pharmaceutical company with no more than 500 employees established no later than 1975 (only one company fell into this latter category)
- University (or government laboratory) that transferred the discovery to a pharmaceutical company,
- University that transferred the discovery to a biotech in the same general region (e.g., within Europe or within N. America) as the university,
- University that transferred the discovery to a biotech from outside the region.

However, I did not rely exclusively on patents and the places of employment of inventors in this attribution process. Instead, the lists of inventors and related articles opened windows on other information about the discovery and development of many of these drugs which I incorporated into the final attributions. Nevertheless, I relied on the key patents as my main identifier and filter for the key discoveries leading to these drugs. Examples how I attributed origins in four complex cases are in the appendix

This analysis uses as an indicator of innovativeness (in terms a drug's response to unmet medical needs and its scientific/pharmaceutical originality) whether it is a new therapeutic biologics (NTB), an NME accorded priority review (pNME) by the FDA, or an NME accorded only standard review (sNME). By administrative definition, priority status is an indicator of innovativeness with respect to meeting medical needs, i.e., drugs are accorded priority review if they offer *substantial benefit over currently marketed drugs*. It is also a reasonable indicator of scientific, technical and conceptual innovativeness. Most of the pNMEs represent previously unapproved classes of chemical compounds, whereas, in the case of most of sNMEs, the FDA has approved at least one other drug in the same chemical class with similar physiologic action.²

In addition, this study identifies the companies that have been instrumental in the post-discovery commercialization of each drug—the first licensees, the New Drug Application (NDA) applicants to the FDA, and the companies that marketed each drug in each of the world's three major pharmaceutical markets following NDA approval. It estimates 2005 world sales for each drug as an approximate indicator of market demand prior to the introduction of generic competitors, and benchmarks sales for each category of drug by region against that region's proportion of the world's ethical pharmaceutical market. Finally it analyzes separately drugs that are designated as *orphans* in the United States and Japan to show how the impact of orphan drug legislation can differ according the larger drug discovery and development environment.

² More details in forthcoming publication.

This analysis is the culmination of research begun in 2005, preliminary results of which have been published in Kneller (2005a&b) and Kneller (2007a). However, it relies upon important research from a variety of fields. These include articles describing the discovery and development of most of these drugs and also studies on the relationship between university research and drug discovery.

This analysis offers insights that should be helpful for the United States, Europe, Japan, as well as countries such as India and China that are now building their pharmaceutical industries, to improve (or maintain) the institutional and business environments that are conducive to the discovery and commercialization of innovative drugs that respond to public health needs.

Findings and analysis

Numbers of new drugs

A significant result of this study is a summary of the breakdown of the 169 new drugs according to type of inventing institution and whether the drugs are sNMEs, pNMEs or NTBs.

sNMEs are most likely to originate from established pharmaceutical companies (75 percent). In contrast, NTBs are most likely to originate in universities or biotechs (88 percent). pNMEs are about equally divided between pharma and non-pharma origin. Overall 68 percent of university discovered drugs were developed initially by biotechs. However, among university-discovered sNMEs, only 47 were initially licensed to biotechs, in contrast to 75 percent of university-discovered pNMEs and 88 percent of university-discovered NTBs. In other words, not only are biotechs important overall for developing university discoveries, but the synergy seems strongest in the case of university drugs offering the greatest health benefit.

A summary of attributions by type of drug, inventing organization and country of origin suggests that, aside from the United States where 64 percent of new drugs originated in universities or biotechs, large pharmaceutical companies discovered the overwhelming majority of drugs in other countries. However, closer examination shows that nearly half of Canadian origin drugs and all Australian drugs were also discovered outside of large pharma. Almost all these Canadian and Australian non-pharma origin drugs were discovered in universities and then biotechs undertook development. As for other countries, the number of drugs discovered either in biotechs or in universities and then licensed to biotechs in the same region is miniscule. The UK can claim about two and a half and Japan one. Provigil® (sNME 1998) was discovered by the small French pharmaceutical company, Laboratoire L. Lafon, which I classified as a *biotech* for the purpose of this analysis. In no other countries did biotechs or small pharma companies discover any drugs or carry out initial development of drugs discovered by universities in the same region. However, out-of-region biotechs (mostly US) have played an important role in early stage development of

university-origin drugs from regions where indigenous biotechs are not prominent, especially in the case of pNMEs. 60 percent of pNMEs from European and Asian universities (including UK and Japanese universities) owe their development to out-of-region biotechs. In probably most of these cases, large pharmaceutical companies were unwilling to develop these drugs. However, these partnerships are limited to pNMEs. In the case of all sNMEs discovered in Asian or European universities, large pharmaceutical companies are the development partners.

As for university-origin drugs per se, the three countries where biotechs are most prominent in drug discovery are also the countries where universities contribute the most to drug discovery.³ In these countries, the percentage of university discovered drugs that are initially developed by pharmaceutical companies is very small⁴ indicating that biotechs have become universities' main development partners for pharmaceuticals in these countries. Somewhat surprisingly, in most other major pharmaceutical countries, university-discovered drugs transferred to pharmaceutical companies, account for about 10 percent of each country's total.⁵ The notable exception is Switzerland, whose university researchers appear to have had no direct role in the discovery of any of its 9.45 drugs. Otherwise in developed countries with some major pharmaceutical companies but weak biotechs, 10 percent may somehow be a common average reflecting the extent to which university and corporate researchers naturally reach out to each other and the proportion of each country's total drug discovery effort that such collaborations represent.

The contribution of European and Japanese universities to drugs transferred to pharma is mainly in the form of sNMEs co-invented with pharmaceutical industry researchers, in other words, sNMEs that arise from collaborative research. The exceptions that are discovered entirely by university researchers tend to be pNMEs. *This suggests that collaborative drug discovery involving universities and established pharmaceutical companies tends to result in drugs that are similar to drugs already on the market, not to ground breaking drugs.*

Israel's drugs (2 sNMEs and 1 NTB) are all from academic institutions and are licensed to either established European or Japanese companies. Israel accounts for a majority of the drugs attributed to *other* countries. It does not have R&D oriented pharmaceutical companies. The licensing practices of Israeli academic institutions may reflect their need to find development partners that have worldwide marketing capabilities, which may favor established companies over biotechs.

3 University origin drugs account for 31 percent, 44 percent and 83 percent of United States, Canadian and Australian origin drugs, respectively. The only other country with an equivalently high proportion is Sweden, 1.8 of whose 3.8 drugs (39 percent) originated in universities.

4 0 percent of Canadian and Australian origin drugs, and 14 percent of US university-origin drugs.

5 UK (9 percent), Japan (7 percent), Germany (9 percent), France (7 percent), Italy (11 percent of 3 drugs), Spain (15 percent of 2 drugs), Finland (5 percent of 2 drugs) and as noted previously, Sweden (39 percent of 3.8 drugs)—Appendix 3.

Is the phenomenon of biotechs (and universities licensing to biotechs) playing such an important role in drug discovery in the United States, Canada and Australia, especially with respect to pNMEs and NTBs, simply a matter of biotechs and universities in these countries substituting for similar discoveries that pharmaceutical companies would otherwise make in these countries—and continue to make in other countries? The relative performance of various countries in terms of discovering sNMEs, pNMEs and NTBs offers insights. To simplify the analysis, I grouped countries as follows: the United States, Canada and Australia (hereinafter UCA), the UK, Japan, Continental Europe, and other. In UCA, biotechs and universities each account for about one-third of drug discovery, and biotechs are six fold more likely than pharmaceutical companies to develop university-discovered drugs. I analyzed the UK and Japan separately. I grouped the countries of Continental Europe together because drug discovery depended almost entirely upon large pharmaceutical companies. Indigenous biotechs did not discover any of that region's drugs. Universities discovered for only 16 percent, and US biotechs ended up developing about 40 percent of these. However, because Swiss pharmaceutical companies discover a large number of NMEs relative to that country's size, I also analyzed Continental Europe without Switzerland, so has to have a better sense of the performance of countries such as Germany, France and Italy and the Scandinavian countries. *Other* consists of 2.3 Israeli drugs, one Chinese pNME, Trisenox® (2000), one Korean sNME, Factive® (2003), and the 15 percent of the pNME, Arixtra (2001), attributable to an Egyptian academic researcher.

As for a benchmark against which to assess numbers of drugs discovered in the various regions, I decided to use each country's or region's share of the world pharmaceutical market, reasoning that this is probably the best single index of a country's capability and incentive for drug discovery. However, I might have used other indices, in particular, GDP. Choosing pharmaceutical sales as my benchmark biases the analysis against the United States. The United States accounts for a disproportionate share of the global pharmaceutical market. In other words, pharmaceutical expenditures as a proportion of GDP in the United States are higher than in most other developed countries, and pharmaceutical expenditures per capita are higher in the United States than any other OECD country by a wide margin. On the other hand, share of world pharmaceutical market underestimates the level of discovery expected from the UK relative to that of other leading pharmaceutical countries. The UK accounts for only 3.4 percent of global pharmaceutical sales, although its GDP is in the same range as Germany and France, which account for 5.6 and 5.8 percent of the world pharmaceutical market, respectively. The UK is the only major pharmaceutical country whose share of the world pharmaceutical market is substantially below its share of world GDP, while the US share of the world pharmaceutical market greatly exceeds its share of world GDP.

With these caveats in mind, there is a remarkably close correspondence between total number of drugs discovered per region and each region's share of the total world pharmaceutical market. The only outliers showing greater than expected drug discovery are the UK (even assuming that its share of total world market should be approximately 5.8 percent), Switzerland (whose contribution can be seen in the difference between the bars

for Continental Europe and Continental Europe (except Switzerland) and Israel. UCA is unique in that over half of drug discovery occurs in biotechs or in universities that license to biotechs, while in other regions, the vast majority of drug discovery occurs in the in-house laboratories of large pharmaceutical companies (blue). So far, this picture is consistent with biotechs/universities *substituting* in UCA for drug discovery that probably would otherwise be done by large pharmaceutical companies.

However, striking differences emerge when analyzing sNMEs, pNMEs and NTBs separately that are inconsistent with mere substitution. UCA's share of sNMEs is considerably lower than expected on the basis of world pharmaceutical market, while those of all other major pharmaceutical R&D regions are higher than expected. In these other regions the vast majority of sNMEs were discovered in large pharmaceutical companies. Universities played a very minor role (except in Israel) and biotech's role was almost negligible. But even in UCA, half of sNMEs were discovered by pharma, compared with 37 percent of UCA drugs overall, while biotech's share of UCA's sNMEs was low compared to its share of total UCA drugs (35 percent compared with 57 percent).

In contrast, UCA's share of pNMEs exceeds its pharmaceutical market share, and over half its pNMEs were discovered in biotechs or in universities that licensed initially to biotechs. The UK's share still exceeds its relatively low pharmaceutical market share. Japan's share is considerably below its world market share, and half its share of sNMEs. In other words, Japanese NMEs are highly weighted towards drugs that are similar to those already on the market—and its pharma-origin NMEs even more so (compare the heights of the blue bars for Japanese sNMEs and pNMEs). The same would be true for Continental European pNMEs without Swiss drugs and university drugs licensed to US biotechs (yellow). This indicates that, *like their Japanese counterparts, established German, French, Italian, Spanish, Belgian, Austrian and Scandinavian pharmaceutical companies tend to discover NMEs that are similar to those already on the market.* Switzerland is the only exception. As can be seen from Appendix 3, its major pharmaceutical companies have discovered a large number of both sNMEs and pNMEs relative to Switzerland's size.

However, Swiss pharmaceutical companies discovered practically no NTBs. Instead, biotechs or universities licensing to biotechs dominate discovery of NTBs. With the exception of Cambridge Antibody Technology which contributed to the discovery of two NTBs, all of these biotechs are based in UCA.

Genetic engineering techniques using microorganisms to produce human-type NTBs were pioneered in universities and then, in a parallel fashion, in industry. However, biotechs rather than pharmaceutical companies took the lead in commercialization and have maintained it. Discovery and development generally takes longer for NTBs than NMEs, and discovery and pre-clinical testing is probably more expensive on average for NTBs. (DiMasi 2007). My own comparison of development histories and key patents indicate that the discovery of NTBs is usually more complex than the discovery of NMEs. One NTB usually embodies components or technologies in-licensed from several institutions. As a

class, more NTBs were approved on a priority basis than NMEs as a whole. The higher average sales for NTBs discussed below also suggests that they meet important medical needs. While these factors do not prove that NTBs as a class are more innovative than NMEs, they do suggest that they tend to be innovative drugs, whether assessed on their response to medical needs or the scientific and technical hurdles to be overcome to bring them to the stage of human testing.

It is interesting to review reports from the 1990s describing how some major pharmaceutical companies were concertedly building in-house capabilities to discover biotechnology drugs (Zucker and Darby (1997a&b), Henderson, Orsenigo & Pisano (1999), Pisano (1996), McKelvey (1996)), in light of their still sparse contributions to approved NTBs. Even though these drugs have high sales and thus the incentives to discover them ought to be high, even the large pharmaceutical companies that appeared to be investing heavily in biotech in the 1980s and early 1990s still have not matched the discovery capabilities of the new companies formed after 1975.

In summary, without biotechs, it is hard to imagine that the pace of discovery and development of NTBs and pNMEs would have been as rapid as it has been. In UCA, biotechs have not only substituted for large pharmaceutical companies in the area of drug discovery. *They have shifted discovery towards more innovative drugs that are more responsive to health needs.*

Sales

Many of the pNMEs address relatively rare diseases for which overall market demand is low. About 43 percent had 2005 global sales under \$100 million, compared with about 30 percent of sNMEs and about 36 percent of NTBs. From a business perspective, it would not be unreasonable if large pharmaceutical companies concentrated their resources on discovering and developing drugs that have high potential sales, thus leaving drugs that address more niche medical needs to universities and biotechs to discover and develop. Therefore, if drugs with low potential sales make up a disproportionate number of pNMEs, it would not be surprising if large pharmaceutical companies tend to discover relatively few of these drugs. Indeed, approximate average 2005 sales for sNMEs and pNMEs discovered in biotechs (or in universities and then licensed to biotechs) are lower than average sales of pharma discovered drugs by a factor of about 2.5. Also the approximate average sales for pharma discovered sNMEs and pNMEs are remarkably similar (about \$525M), as are the averages for sNMEs and pNMEs discovered by biotechs, or universities then licensed to biotechs (about \$205M). In other words, on the surface it seems that the distinction between sNMEs and pNMEs may matter little with respect to what type of organization is likely to discover them. Large pharmaceutical companies seek to discover drugs that are likely to have high sales, while biotechs and universities are left to discover the rest. Although this may have implications for public health (particularly the health of persons with rare diseases), from a business perspective it is not surprising.

However, when NTBs are included, the approximate average 2005 sales of biotech origin drugs are much closer to those of pharma origin drugs (\$529M vs. \$465M).

Furthermore, when only drugs originating from UCA are analyzed (the only region where biotechs are active in drug discovery), approximate average biotech vs. pharma sales are almost identical (\$553M vs. \$502M). Moreover, an interesting phenomenon emerges with approximate average 2005 sales of biotech origin drugs increasing as one moves along the continuum from sNMEs to pNMEs to NTBs--arguably a continuum representing increasing responsiveness to medical needs and increased scientific challenge related to discovery. In contrast, approximate average sales of pharma-origin drugs are highest for sNMEs and decline significantly for pNMEs (\$403M). In other words, rather than the simple market-determined dichotomy, in UCA, biotechs are significant actors in the discovery of drugs that not only respond to unmet medical needs and are scientifically challenging to discover, but also have high market demand.

An analysis for sales for numbers of drugs again shows (perhaps surprisingly) that sales attributable to drugs originating in each of the regions are remarkably close to each region's share of the world pharmaceutical market, except again for the UK. However, sNMEs discovered in Japan and Continental Europe (almost all in pharma labs) account for a much greater share of total world sNME sales than would be predicted on the basis of these regions' shares of the total world pharmaceutical market. Conversely, UCA's share of total sNME sales is lower than expected. Moreover, sNMEs discovered in biotechs (or in universities then transferred to biotechs) account for only a small fraction of these sales.

In the case of pNMEs, Continental Europe's strength has disappeared, except for sales of pNMEs discovered by Swiss pharmaceutical companies. Moreover nearly half of sales of pNMEs discovered in Continental Europe ex-Switzerland, are attributable to two drugs co-discovered by Belgian and Czech academic scientists and licensed to Gilead (Viread® and Hepsera®) or contributions by university researchers whose discoveries were transferred to major pharmaceutical companies. *German, French and other non-Swiss European pharmaceutical researchers simply did not discover pNMEs that have substantial sales.*⁶

The situation may appear different for the UK and Japan, but these countries' high sales are accounted for sales of just two blockbusters each: Avandia® and Viagra®, which together account for 82 percent of sales of UK-origin pNMEs,⁷ and Actos® and Eloxatin® which account for 97 percent of sales of Japanese-origin pNMEs.⁸ Eloxatin® was discovered in Nagoya City University. A metals company did important development work, but no

6 With the exception of Zometa to whose discovery both Boehringer Mannheim and Ciba Geigy contributed approximately equally.

7 Avandia, discovered by Beecham scientists and approved in 1999 for diabetes, had 2005 sales of \$2.1B. Viagra, discovered by scientists in Pfizer's Kent laboratory and approved in 1998 for erectile dysfunction, had 2005 sales of \$1.6B.

8 Actos, discovered by Takeda scientists and approved 1999 for diabetes, had 2005 sales of \$2.4B. Eloxatin (2002) had sales of \$1.9 B.

pharmaceutical company would sponsor clinical trials for this cancer drug. Eventually a Swiss biotech, DebioPharm, raised funds to in-license the drug and sponsor trials.

In contrast, not only are sales of UCA-origin pNMEs fairly close to levels predicted by that region's share of the world pharma market, and not only do biotech/university-discovered pNMEs account for over a third of those sales, those sales are much less concentrated in a few blockbuster drugs (data not shown), whereas only three such mid-range sales pNMEs were discovered by Japanese and UK/European (ex-Swiss) pharmaceutical companies.

As for NTBs, drugs discovered in UCA biotechs or UCA universities and transferred to UCA biotechs dominate sales. These include the two drugs with the highest 2005 sales among all 169 drugs, Remicade® (1998) for rheumatoid arthritis and Crohn's disease (\$4.8B) and Aranesp® (2001) to counter anemia (\$3.3B). However, not all of these are blockbusters. About one-third of these drugs have sales under \$100M.

In summary, outside of UCA, not only is drug discovery confined mainly to large pharmaceutical companies (with a roughly 10 percent contribution from universities that transfer directly to large pharmaceutical companies), but also drug discovery leading to marketed drugs is limited mainly to drugs similar to those already on the market, except in Switzerland and in the case of a small number of innovative drugs that have potential to become blockbusters. *This suggests a risk adverse drug discovery and development strategy on the part of established pharmaceutical companies that focuses resources on already proven classes of drugs, except for a few projects aimed at innovative compounds for high-demand markets.*

In contrast, in UCA, biotechs excel in the discovery of more challenging and more medically needed areas of drug discovery. UCA biotechs account for the vast majority of NTB worldwide sales and also a significant proportion of UCA-origin pNME sales. But another distinctive feature of drug discovery in UCA is that UCA pharmaceutical companies, unlike pharmaceutical companies in other regions (Switzerland excepted), also discover pNMEs with mid-range sales, mostly for infectious and ophthalmologic diseases.

Underlying factors

This analysis does not prove that the presence of biotechs, per se, is the crucial factor in spurring the discovery of pNMEs and NTBs. It is also possible that some other factor, unique to UCA, both encourages the discovery of such drugs and enhances the environment for biotechs. Two possibilities are the high levels of public support for academic biomedical R&D (in the United States, mainly through NIH), and the mechanisms by which such support is distributed (for example, high quality peer review of grant applications with a large percentage of funds directed to investigator initiated projects rather than large multi-researcher projects). Indeed, US government support for health related R&D does constitute a higher percentage of GDP than equivalent funding levels by other governments, well over twice the percentages for Japan and major Continental European countries (data not shown). Canada, where biotechs are also active in drug discovery, is probably closest to the United States in terms of the proportion of GDP accounted for by government support for biomedical research. Also, at least in Japan, the

manner in which government funds are allocated does not involve the same degree of careful, expert-based consideration of competing research proposals as does the US NIH system of grant review. The same applies to the system of recruitment, promotion and support of young researchers in Japan compared to the system in US universities. It is still harder in Japan for bright, energetic young researchers to establish their own base for independent research in Japan (and perhaps European countries as well) compared to the United States (Kneller 2007b and other chapters in same publication).

The fact UCA pharmaceutical companies appear better than their ex-region counterparts in discovering pNMEs with mid-range sales suggests that government support for basic biomedical research may indeed be producing discoveries upon which pharmaceutical, as well as biotechs, are building innovative drug discovery programs—without having to aim exclusively at blockbuster potential pNMEs.

But even if government support for biomedical R&D and the way it is distributed are major factors underlying the discovery of larger than expected numbers of pNMEs and NTBs, the fact remains that biotechs have been crucial in turning government funded research results into actual drug discoveries (or in carrying forward early stage development of discoveries made in universities). If government funding alone was the major factor, why have not pharmaceutical companies taken advantage of this and become leaders in pNME and NTB discovery in UCA as well? With all their resources, why have they left it up to biotechs and universities in this region to discover a majority of the drugs that are most innovative and most responsive to health needs? Perhaps it is the combination of generous, well-allocated government funding—coupled with a variety of social, institutional and financial factors that create a supportive environment for new companies—that have made biotechs particularly well suited to discover and develop drugs based upon pioneering university research. At the same time, large pharmaceutical companies may have realized that it makes business and even scientific sense for them to rely to universities and biotechs (and the capital markets that fund them) to assume the risks associated with discovering innovative drugs and bringing them to proof of concept stage.

However, the phenomenon of biotechs supplying large pharmaceutical companies with drugs that have achieved proof of concept applies to less than half of biotech/university origin drugs. In the case of 62 percent of the drugs discovered by a biotech (or in a university that licensed to a biotech), that same biotech completed clinical trials and submitted the application for marketing approval to the FDA. In the case of one third of biotech/university drugs, the same biotech was marketing the drug in at least one of the world's major markets more than one year after receiving marketing approval. In other words, a substantial proportion of these biotechs made long term commitments not only to the discovery but also to the development and marketing of their drugs. This commitment is greatest among the discoverers of pNMEs and NTBs (data not shown).

The reverse phenomenon of biotechs applying for NDAs on drugs discovered in pharmaceutical companies was just as frequent as pharmaceutical companies applying for

NDA on biotech/university discovered drugs. In other words, biotechs are also playing an important role in bringing to market pharmaceutical origin drugs that have low sales prospects but offer improved health benefits.

There is little evidence that biotechs being the primary developers of university discovered drugs in UCA stems from universities licensing preferentially to startups rather than to pharmaceutical companies. Large pharmaceutical companies often decline to license early stage drug candidates or targets from universities, which end up licensing these to biotechs as a last resort (Shane 2004). Pharmaceutical executives say that if they have the option to develop university and in-house-discovered candidate drugs for the same disease, they prefer to develop the in-house compounds, because they retain greater control over the latter. Licensing officials at the US NIH report that most licenses for NIH-discovered candidate drugs or drug targets are now licensed to biotechs, which represents a change from the 1980s and early 1990s.⁹ Senior product development managers in one of the largest US pharmaceutical and medical device companies told me in 2006 that in both fields their company also has come to rely mainly on biotechs for new technologies, many of these being university startups.

In other words, the fact that most innovative discoveries from UCA universities are being developed by biotechs rather than pharmaceutical companies probably is not due to biotechs pre-empting discoveries that pharmaceutical companies want to develop or to preferential licensing from universities to startups or other biotechs.¹⁰

Orphan drugs

In 1983, the United States became the first country to enact orphan drug legislation to provide incentives to develop drugs to treat diseases that affect fewer than 200,000 Americans a year, or whose development costs cannot be covered by sales in the U.S. The

⁹ The director of licensing at the NIH Office of Technology Transfer remarked, “Big pharma is simply not interested in early stage licenses.” (personal communication, 2006) When I worked in biomedical research and technology transfer in NIH from 1988 to 1997, a substantial proportion of such licenses did go to established pharmaceutical companies.

¹⁰ However, at least in Canada’s case, an additional factor may be explicit policies by both national and provincial governments to foster the growth of innovative new companies so as to keep as much of the value added development of Canadian university discoveries in Canada. According to one of the senior directors of the University of British Columbia’s technology development office, because Canada does not have large pharmaceutical companies, fostering the growth of indigenous biotechs (and, to some extent, startups in other industries) that will develop university inventions, is the only alternative to licensing such discoveries to foreign companies. I am not sure if similar policies are influential in Australia. Even in the United States, regional develop objectives sometimes favor licensing to local startups. Also the Bayh-Dole law (35 U.S.C. §§ 200-212) and the applicable regulations (37 C.F.R. § 401.14(k)(4)) calls for licensing of US Government funded university inventions preferentially to small businesses (companies with no more than 500 employees). Nevertheless, based upon the totality of evidence of which I am aware, these preferences probably do not result in many university pharmaceutical discoveries being licensed to biotechs when pharmaceutical companies were also competing for a license.

key incentives are seven years exclusivity for the orphan indication in the US market¹¹ and tax credits up to 50 percent of the cost of clinical trials. Between 1983 and 2005, the FDA conferred orphan status on 282 drugs and biological products. In contrast only about 10 drugs for rare diseases were approved by FDA and brought to market in the decade before enactment (Haffner 2006). However, as described in detail in a forthcoming publication, the discovery and development of orphan drugs for the US market, particularly pNMEs and NTBs depends overwhelmingly on universities and US biotechs. Even marketing of orphan drugs relies mainly on biotechs.

Japan and the European Union followed with similar legislation in 1993 and 2000, respectively. On the basis of the US experience such legislation might have been expected to encourage local or regional companies (perhaps primarily biotechs) to discover orphan drugs for the local populations.

However, of the 37 drugs that the Japanese pharmaceutical regulatory authorities accorded orphan drug status between 1998 and 2003, only three were new drugs originating in Japan. Only one originates from a university or new company, and another will likely be approved for a non-orphan indication. The vast majority (76 percent) of the drugs accorded orphan status by Japanese authorities were new drugs discovered overseas, while the remaining 16 percent were old drugs for which approval for orphan applications was being sought.

Thus in contrast to Japan's two or three new orphan drugs, over the same period, the number of US discovered new orphan drugs grew by 21, less than three of which are attributable to pharmaceutical companies. Although the US Orphan Drug Law may have been an important factor behind the large number of US pNME drugs being discovered and developed for niche needs, primarily by biotechs, *the Japanese experience suggests that simply implementing orphan drug legislation will not necessarily result in the discovery of many innovative drugs, or in the rise of more biotech companies.* Other factors are necessary to promote pharmaceutical innovation in niche areas.

Could the situation with respect to orphan drugs be different in Europe? Could there be a significant number of innovative drugs for niche markets that have not been approved for the US market? I hope researchers with access to European orphan drug approval data will answer this question definitively, although the issue may be moot in terms of the 1998-2003 period since the European orphan drug regulations only went into effect in 2000. Nevertheless, among the FDA approved orphan drugs, four were invented in Europe, yet companies sponsored them in the United States, despite the prospect of low sales. In other words, a variety of companies (US as well as non-US) have shown they can conduct viable businesses developing and marketing drugs for niche markets. As the United States is the largest market for most of these indications, it might be reasonable to assume that orphan drugs that are discovered overseas and shown to be effective would eventually be marketed

¹¹ i.e., the FDA will not approve another application for the same drug to cover the same disease, an important protection because many orphan drugs are not covered by patents.

in the United States. Thus the number of orphan drugs emerging from Europe probably is also low, although this may change as a result of the 2000 European legislation.

Main Conclusions and Limitations of this Study

Public Health

This study shows that new companies (biotechs) and universities that license to biotechs, account for the discovery of at least half of the new drugs that respond to unmet medical needs and also at least half the drugs that are first in class compounds and that are the most scientifically innovative. These companies are located almost exclusively in the United States, Canada and Australia, with a few in the UK, one in Japan and none in Continental Europe. The contrast between the types of drugs discovered in regions where there are few biotechs and in regions where they are active in drug discovery indicate that biotechs and universities are not simply substituting for drug discovery that would otherwise occur in established pharmaceutical companies. Neither can a simple division of drug discovery efforts according to market size, with pharmaceutical companies pursuing discovery of drugs with high sales potential and leaving the low sales drugs to be discovered by biotechs and universities, explain the observed patterns. Rather, the sales data are consistent with established pharmaceutical companies, especially those outside the United States, concentrating discovery and development efforts on low risk, non-innovative drugs, except for a few innovative drugs that have blockbuster sales potential. Even so, they have not been able to match the new biotechs in discovering NTBs, which have the highest mean sales of all classes of drugs. *Without biotechs, the number of new innovative drugs that meet unmet medical needs would probably be significantly less than it is today.*

Limitations

The major limitation of this study is that, because it focuses only on drugs approved by the FDA for the US market, it inevitably misses drugs originating in Europe and Japan that have not were not submitted for NDA approval. In terms of the validity of the main conclusions of this study, the most crucial issues are the proportion of these missed drugs that had university or biotech inventors and the proportion that would be classified as pNMEs or NTBs. In other words, if the almost all the missed drugs were discovered by pharmaceutical companies and would be classified as sNMEs, the overall regional proportions and average sales might change, but the basic findings would not. Even if a significant proportion of the missed drugs did have university inventors but most of these drug are sNMEs, the basic conclusion that vibrant biotechs with close ties to universities discover a disproportionate number of innovative drugs that respond to unmet health needs would not change. In fact, if such sNMEs were co-invented by pharma and university researchers, it would bolster the observations at notes 2-4 and accompanying text that collaborative university-pharma drug discovery research tends to lead to non-innovative drugs.

I know of quite a few Japanese drugs for which overseas marketing approval has never been sought, including a few whose discovery did involve input from university researchers. Although I cannot speak for the FDA, it seems unlikely that many would be classified as pNMEs. In addition, the fact that US marketing approval is being sought for at least two of the three Japanese orphan drugs newly approved in Japan suggests that, even if patient populations are low, companies will step forward to sponsor them for FDA approval if they are likely to meet medical needs. The case of one of these Japanese origin orphan drugs, Amnolake®, illustrates how a drug discovered by Japanese university researchers who had difficulty finding any Japanese company to undertake development and which has only low-to-modest sales prospects, was licensed within a few years of its approval in Japan by a United States biotech which is now working to obtain FDA approval. Thus it is probably reasonable to assume that the number of drugs discovered in Japan and Europe for which marketing approval in the United States has not been sought, but which the FDA would likely classify as of pNMEs or NTBs, is quite low.

Another major concern is that I may have missed some significant contributions by university researchers (or less likely by biotechs) to the discovery of some of the drugs. The various steps described under methods (particularly the use of multiple data sources such as the patents listed in the FDA correspondence, patents and articles listed in the Merck Index, Rader's (2006) histories of the development of all the NTBs, SEC filings, and various scientific and business articles) are all intended to decrease this likelihood as close as possible to zero. Nevertheless, I learned about Brian Drucker's contribution to the discovery and development of Gleevec® (pNME, 2001) and the University of Minnesota's to the discovery of Ziagen® (pNME, 1998) not from my main data sources but in the process of reading articles related to this drug. Because I have less access to non-English language articles, I may have missed similar references to Continental European academics making similar contributions to the discovery of some Continental European drugs.

The caveats related to relying on priority review and NTB status as surrogates for innovativeness are discussed in a forthcoming publication, as are the limitations in relying on 2005 sales to as surrogates for overall market value and uncertainties about some of the sales data.

This analysis only extends to drugs approved through 2003. It is possible that including drugs approved in subsequent years would show different trends. However, I was struck by how many of the key patents for pharma-discovered drugs approved between 1998-2003 were filed in the 1970s or early 1980s before biotechs had emerged on the scene.

There are conceptual (even philosophical) issues about how to define and assess discovery and innovation. In preliminary analyses (Kneller 2005a&b), I focused only on patents. But as noted under *methods*, a better approach is to integrate information on the patent inventors with scientific articles often written by the same inventors. It was reassuring that, in many cases, both the articles and patents indicated the same researchers/organizations were responsible for the discovery of the core active compounds and/or proof of concept.

Nevertheless, I had to make judgment calls when researchers in more than one organization contributed significantly to discovery, as was the case with 16 NMEs and over half the NTBs.

Finally, discovery of the core compounds is only one aspect of pharmaceutical innovation—perhaps not even the most important or difficult part. Even more important may be corporate recognition of a medical need and a commercial market and the decision to push ahead with development of a candidate drug. In this sense, my emphasis on identifying the inventors of key compounds ignores an important part of the drug discovery and development picture.¹² It also overlooks the often significant challenges in altering the basic compounds to make them more effective, safer and easy to manufacture and use, as well as the challenges in conducting human trials. Finally it overlooks key contributions in basic science such as elucidation of key genes, proteins and metabolic pathways (usually from universities) as well as natural product discovery programs, screening systems, and the development of assay systems, culture systems, animal models, etc. by universities, government laboratories such as NIH and FDA, biotechs and pharmaceutical companies.

national innovation systems and alternatives to biotechs as innovation leaders

This paper concludes with two questions that have so far remained in the background:

- What is it about biotechs that tends to make them more innovative (at least as a group) than established pharmaceutical companies, or, more generally, what is it about the innovation systems in North America and Australia that enables biotechs to be engines of innovation?
- In countries with different innovation systems, where biotechs are unlikely to become major engines of drug discovery in the near future, what alternatives are there to increase discovery and commercialization of innovative drugs?

Regarding the first, the close relations between biotechs and universities provide a partial answer. Human factors and the contrasting cultures of small or new vs. large and established organizations probably also play a role. In other words, there are probably factors particular to an entrepreneurial (i.e., new and relatively small company) setting that motivate founders, managers and researchers to work concertedly on the projects at the core of the biotech's business (Kneller 2007a). Recent surveys of employee job satisfaction show biotechs generally scoring higher than established pharmaceutical companies (Pallarito, 2006). Furthermore, the combination of generous and astutely allocated US government support for biomedical research (at least compared to the way government

¹² I thought for some time whether it was appropriate to attribute one quarter of the development of Gleevec® to Brian Drucker, who was not an inventor on any key patent, but whose main contribution was to point out its value in treating some forms of leukemia and some other tumors, to develop assays to measure its effectiveness and to encourage Novartis to proceed with clinical trials. I stuck with this allocation to try to give appropriate credit to someone who was responsible for pointing out the importance of this class of compounds and for pushing forward Gleevec's early development. However, I may have missed similar contributions to some other drugs by university, biotech or pharma researchers.

support is allocated in some other industrialized countries), the large number of young scientists (including immigrants) trained as a result of this support, and a supportive societal and institutional environment for entrepreneurial companies, results in large numbers of capable scientists joining biotechs to satisfy their career aspirations. This supportive institutional environment includes:

- relatively plentiful venture capital, angel and other forms of financing in the United States and Canada,
- open immigration policies (at least until 2001, as far as the United States is concerned),
- an open innovation stance on the part of large companies in marked contrast to the autarkic innovation strategy that still characterizes Japanese in-house pharmaceutical research (and perhaps also that in many Continental European companies),
- the Bayh-Dole amendments to US patent law that facilitated the exclusive licensing of government funded university inventions—exclusive rights being extremely important for the formation of biotechs focused on drug discovery,¹³
- university technology management policies in the United States, Canada and Australia that generally are supportive of startups (again in marked contrast to Japan where such policies favor exclusive transfers of university discoveries to established companies) and,
- perhaps most importantly, high labor mobility as opposed to the lifetime employment which still prevails in most large Japanese and Continental European manufacturing companies and is antithetical to the needs of biotechs engaged in high risk drug discovery and development (Kneller 2003 & 2007a, Hyde 2003, Casper 2000).

In regard to financing and in particular to labor mobility, it is probably no coincidence that the United States, Canada and Australia are all characterized as having *liberal market economies* as opposed to *coordinated market economies* found in Japan and Continental Europe. The former are characterized by high labor mobility, minimal government and organized labor involvement in business decisions, and a tendency for equity as opposed to loan financing for business expansion; while the opposite features characterize coordinated market economies. (Hall & Soskice 2001) Without delving deeply into a *varieties of capitalism* analysis, one hypothesis emerging from this distinction is that liberal market economies tend to support innovation in new companies while coordinated market economies tend to confine innovation to old companies. At least this seems consistent with the contrasting patterns of drug discovery in UCA compared with Japan and Continental Europe. Indeed, the main differential impact on innovation of liberal vs. coordinated market economies may be that the former encourage breakthrough innovations by new companies while the former encourage incremental innovation by large, established companies (Kneller 2007a).

¹³ While Bayh Dole has been criticized for causing some US universities to over emphasize on license revenues (Leaf, 2005) and Mowery et al (1999) have noted that university biomedical patent applications began to rise even before its enactment, a sharp rise in the formation of therapeutic oriented biotechs began after its enactment in 1980 (Kneller 2007a).

However, the decision making process in even the best managed large organizations may inevitably increase risks that new projects will be overlooked or abandoned—largely because of a natural (and probably rational) tendency to focus on products and research methods that have proven successful and the needs of current customers. This phenomenon has been well documented in the case of the IT industry (Christensen, 1993) but also in the case of pharmaceutical companies (Zucker and Darby, 1997b). It is echoed in the history of the development of Eloxatin® and more recently Amnolake® and the paucity of pNMEs and NTBs discovered in Japanese and Continental European pharmaceutical companies.

Time will tell if the environment for biotechs will improve outside UCA. Japan has taken significant steps to improve the environment, and it probably now has about 25 biotechs with drugs, drug delivery systems, or regenerative medicine therapies in clinical trials. Nevertheless, in crucial areas such as access to skilled researchers and managers and financing, and the willingness of its own pharmaceutical companies to partner with domestic biotechs on mutually beneficial terms, much improvement is still needed.

Instead, aside from acquiring more overseas-discovered drugs through acquisitions or licensing, the main strategy being pursued by major Japanese pharmaceutical companies to improve drug discovery is to engage in joint research with Japanese universities. Astellas recently announced a ten year large scale partnership with Kyoto University Medical School to discover NMEs and NTBs to treat autoimmune, cancer and other diseases. However, this collaboration was initiated with substantial government co-funding, raising questions about how much public pump priming should be devoted to industry-university joint/translational research projects. Again, time will tell whether these large scale pharma-university partnerships will pay off in terms of innovative drugs—or whether, in keeping with past trends, most of the drugs that emerge will be sNMEs.

Another strategy being pursued by some pharmaceutical companies is to de-emphasize blockbuster drugs and concentrate more on drugs that target niche diseases or patients with specific characteristics, and thus are not expected to be prescribed for large numbers of patients (Frantz, 2005). Such a targeted approach ought to produce more drugs that have innovative mechanisms of action and address unmet medical needs. Whether established pharmaceutical companies will rely mainly on acquiring such lead compounds from biotechs and universities or will discover them in their own laboratories remains to be seen.

For the time being, however, in the interest of public health and to ensure public benefits from public support for biomedical research, it is incumbent upon the United States, Canada, Australia, where biotech entrepreneurship is strong, to maintain a supportive environment for entrepreneurship in this and other high technology fields. It would seem wise for other countries to improve their environments for high technology entrepreneurship.

Appendix:

Case studies illustrating how I made some of the toughest attribution calls.

1. Gemtuzumab ozogamicin (**Mylotarg®**, approved 2000) is a guided-warhead anti-cancer drug consisting of an anticancer drug (ozogamicin) attached to a monoclonal antibody (gemtuzumab) designed to bind to myelocytic leukemia cells. Researchers in Lederle's (now Wyeth's) Pearl River, New York, laboratory designed the anticancer drug and the means to attach it to the antibody and were responsible for the overall design and testing of the drug. Lederle/Wyeth researchers received the 2004 Discoverers Award from the Pharmaceutical Research and Manufacturers of America (PhRMA) for their development of Mylotarg—the first such warhead tipped antibody cancer drug approved by the FDA.¹⁴ Their discoveries related to the anticancer drug are represented by three independent patents listed in the AC. Their discoveries related to linking the anti-cancer drug to the antibody are covered by three other patents listed in the AC, all of which originate from the same application. According to Rader (2006), the antibody to the CD33 receptor (which tends to be expressed uniquely on the surface of myelocytic leukemia cells) originally came from the Frederick Hutchinson Cancer Research Center in Seattle, but CellTech in Berkshire, England, took the lead in humanizing it using its own technology and technology in-licensed from Protein Design Laboratories (PDL) of Mountain View, California. In addition to the six patents assigned to Wyeth, the AC lists two patents assigned to PDL. However, these are not specific for an anti-CD33 antibody. The AC lists no patents assigned to CellTech. However, an article (Hamann et al 2002) co-authored by ten Wyeth researchers, one CellTech researcher and two Fred Hutchinson researchers describes the development of Mylotarg.

One of the four inventors on Lederle's first patent (US 4970198) covering the anti-cancer drug, David Lebeda, was working at the US Department of Agriculture's Northern Regional Research Center in Peoria, Illinois, at the time of the patent application in the mid 1980s. Lederle scientists obtained the microorganism that was found to produce calicheamicins, the family of anti-cancer compounds from which they derived ozogamicin, from the culture collection where Lebeda worked. Thus I assume Lebeda played a key role in providing the microorganism. However, he is not an author on any publications in the PubMed data base that are related to the Mylotarg or its components. Thus, I assume he did not play a major role in elucidating the anticancer properties of calicheamicins or in deriving ozogamicin from them. As for the other inventors listed on the Lederle patents, I confirmed that all were employed by Lederle/Wyeth on the basis of publications or a clear history of assigning patents to Lederle, Wyeth, or American Cyanamid (Lederle's parent until the name was changed to Wyeth).

In attributing discovery to the various laboratories, I weighted inventing/developing the warhead, the linker, and the antibody, and integrating all of these into a prototype drug,

¹⁴ I do not know why Mylotarg was approved as a pNME rather than an NTB.

0.25 each. Taking all the above factors into account, I attributed the warhead, linker and integration to Lederle and thus attributed **75 percent** of the discovery to **US pharma**. Of the remaining 25 percent attributable to the antibody, I allocated **15 percent** to CellTech researchers (**UK biotech**) because they seem to have played the main role in humanizing the antibody. I allocated **5 percent** to PDL (**US biotech**) because CellTech relied to a considerable degree on PDL's technology for humanizing antibodies and, even though PDL's technology probably was not specific to CD33 receptors, Wyeth evidently thought that PDL's patents covered the antibody when it submitted its application to the FDA. Finally I attributed **5 percent** to Fred Hutchinson (**US university licensing to out-of-region biotech**) whose researchers developed the original mouse antibody against CD33. I ignored Lebeda's/USDA's contribution, although if the patent/development record had involved fewer contributors and was less complex, I would probably have attributed a small proportion of the discovery to "US university licensing to pharma."

2. Tenofovir disoproxil fumarate (**Viread®**, 2001) is an antiviral agent, specifically a reverse transcriptase inhibitor to treat HIV/AIDS. Six patents are listed in the FDA AC. The first (US 4,808,716 first filed in Czechoslovakia in 1985) was issued to the Czech Academy of Sciences (CAS) in Prague where its two inventors worked. It covers a class of compounds that exhibit antiviral properties. The second (US 6,057,305 filed in 1992) is issued jointly to the Czech Academy of Sciences and the technology management office, Stichting Rega v.z.w., of the Katholieke Universiteit Leuven (KUL), Belgium. Its four inventors consist of the same two Czech inventors as on the first patent and two researchers at KUL. It covers a subset of compounds under the first patent that "unexpectedly showed activity specifically against retroviruses," and it specifically claims their use against HIV and the hepatitis B virus. The final four patents are issued to Gilead Sciences in California. Three (US 5,922,695, 5,977,089, 6,043,230) originate from the same application filed in 1996. Each of these three patents had the same six inventors, two of whom were US university researchers. (The '695 patent is the single patent listed in the Merck Index.) The fourth (US 5,935, 946) was filed independently in 1997. It has three inventors, two of whom were definitely Gilead researchers. The third inventor, John D. Munger, Jr., although having worked at the U of Nebraska in the 1980s, may have been a Gilead employee when he contributed to this invention. The Gilead patents claim intermediates (pro-drugs) of the compounds claimed in the two earlier European patents that make oral administration of the drug more efficient.

Keeping with the emphasis in this analysis on conceptual breakthroughs that point to discovery and suggest paths for further development, not on the often equally challenging tasks of refining the initial breakthroughs so that the drugs are more easily absorbed by the body, are more stable, more easily manufactured, etc., I weighted the two European patents 0.45 each, and the four Gilead patents together only 0.1.

Considering that about 30 percent of the Gilead inventors were university researchers, I could have attributed this invention 93 percent to *universities transferring to biotechs* and 7 percent to *biotechs* (in-house). However, as in the case of Mylotarg, I was reluctant to parse

origins extremely finely (feeling that my allocations could be reasonably accurate to only one decimal place or perhaps one 5/100ths). Also, in this particular case, it seemed probable that Gilead was taking the lead in developing compounds that had improved oral availability and that the university inventors were probably brought into this development effort because of their expertise in specific fields of medicinal chemistry. With these considerations in mind, my final allocation of origin was **0.9 to university transferring to out-of-region biotech, and 0.1 to biotech**. Attribution by country was **0.9 to Other Europe (attributed roughly equally to the Czech Republic and Belgium) and 0.1 to the United States**. (See also the following.)

3&4. Remicade® and Humira® are both monoclonal antibodies against tumor necrosis factor (TNF) which is implicated in the inflammation that causes rheumatoid arthritis (RA) and other autoimmune diseases. Remicade is a recombinant, chimeric (partially humanized) mouse antibody approved in 1998 to treat Crohn's disease and in 1999 for RA, while Humira is a recombinant, fully human antibody approved in 2002 for RA.

In the case of **Remicade**, at least ten US patents with the same two New York University (NYU) and same four Centocor inventors claim chimeric anti-TNF antibodies or describe the use of such antibodies to treat RA. These patents all trace their origins to the same application filed in March, 1991. A list of all 32 US patents assigned to NYU that have Jan Vilcek as one of the inventors (Vilcek and Junming Le are the two NYU inventors whose names appear consistently on these patents), indicates that probably all of these 32 inventions that deal with TNF antibodies as RA therapy had Centocor co-inventors (most often, the same four Centocor inventors). A 1995 scientific article showing that chimeric TNF antibodies protect mice from TNF-mediated diseases was co-authored by seven Centocor and two NYU researchers (including the same six who are co-inventors on so many related patents) as well as one researcher at the Hellenic Pasteur Institute in Athens (Siegel, 1995). In other words, the patent and publication record suggests a long history of cooperation between Centocor and NYU related to Remicade, along with consistency in terms of the individual researchers involved in this collaboration. Rader's (2006) history indicates Remicade was developed by Centocor in collaboration with NYU researchers. Centocor, based in Malvern, Pennsylvania, was an independent biotech until 1999 when it was bought by Johnson & Johnson in 1999. These factors lead me to attribute the discovery and early stage development of Remicade **2/3rds to Centocor (biotech) and 1/3rd to NYU (university, transfer to biotech)**, and **100 percent to the United States** in terms of national origin.

Humira arose from collaboration between Knoll Pharmaceuticals and Cambridge Antibody Technology (CAT) in the UK (Rader, 2006). CAT developed and provided the phage display technology that enabled creation of a fully human anti-TNF monoclonal antibody. Rader (2006) lists US 6090382 and 6258562 as the two key patents covering Humira. These patents originate from the same application filed in Feb. 1996. Both have the same twelve inventors. Six were working at BASF/Knoll's research center in Worcester, Massachusetts, from the mid 1990s. Six were employees of CAT around the same time,

although one of these, Hendricus Hoogenboom, had in 1995 become an associate professor in the University of Maastricht in the Netherlands, and some of the CAT inventors had ties with Cambridge University—CAT being a Cambridge startup. In the 1990s, Knoll Pharmaceuticals was BASF's US pharmaceutical research laboratory. BASF sold its pharmaceutical operations, including its Massachusetts research center, to Abbott in 2001. Abbott sponsored Humira's application for approval by the FDA and markets Humira worldwide except for Japan where it co-markets with Eisai.

However, PepTech, a UK-Australian biotech company founded in 1985, has patents covering monoclonal antibodies to TNF (e.g., US 5644034 and 6593458, many of which originate from Australian patent applications filed in 1989). Knoll licensed these antibodies for use in Humira. The extent to which Knoll actually relied on PepTech's discoveries is not clear. PepTech's research on TNF antibodies dates from 1988 (Rader, 2006). Articles on this topic by Peptech scientists began to be published around 1991 (see Rathjen, 1991) and the first of Peptech's US TNF antibody patents (no. 5644034) was issued in Nov. 1994, nearly 1.5 years before BASF applied for its Humira patents. Therefore, I assumed that Peptech's TNF antibody technology was in fact used by Knoll to develop its TNF antibodies. One of the two inventors of Peptech's US patents, Roger Aston, served as CEO of CAT before becoming Peptech's CEO in 1995 and had other close links with the UK, reinforcing the likelihood that Peptech's technology played a role in the discovery of Humira. However, the balance of evidence suggests that Roger Aston's work on TNF antibodies was centered at Peptech in Australia. Taking these factors into consideration, I attributed 40 percent of Humira's discovery and early development to CAT (and concluded that all its inventors did their relevant work in the UK), 40 percent to Knoll (and concluded that all its inventors did their relevant work in the United States), and 20 percent to Peptech (and concluded that all its inventors did their relevant work in Australia). Thus my final attribution, in terms of type of discovering organization was **.6 biotech and .4 pharma**, and in terms of national origin, **.4 UK, .4 United States, and .2 Australia**.

Centocor also licensed Peptech's TNF antibody patents. In 2002, Centocor's new parent, Johnson & Johnson, decided Remicade was not infringing these patents and stopped royalty payments, as did Abbott in the case of Humira. The dispute with Abbott was resolved quickly, largely in Peptech's favor (Rader, 2006). But the dispute with Johnson and Johnson was not resolved until the end of 2004, and although it involved some payments to Peptech, the details are confidential and the overall balance of the settlement is not clear. The academic articles co-written by NYU and Centocor describe their own methods for making TNF antibodies and appear to make no reference to articles by Peptech researchers (see Knight, 1993). Although this may have been deliberate, it nevertheless suggests that, to the extent the Centocor and NYU researchers made use of Peptech's discoveries, they made use of knowledge that was publicly available, regardless of whether the techniques were protected by Peptech's patents. Also Centocor/NYU's work was earlier in time compared to Knoll/CAT's. Furthermore, in Roger Aston, there was a clear human link between Peptech and CAT, which likely directly informed CAT's cooperation with Knoll to develop

the anti-TNF antibody that became Humira. For these reasons, I did not attribute any of Remicade's origins to Peptech, although I did in the case of Humira.

For similar reasons, I did not attribute any of Remicade's or Humira's origins to the Weizmann Institute in Israel, which also invented mouse TNF antibodies. (See US Patent 6090923 issued in 2000 claiming priority to applications filed in Israel in 1984.) Through a research alliance with Weizmann, the Swiss pharmaceutical company Serono obtained control over these patents. In 2000, Serono issued licenses to Centocor and Knoll covering Remicade and Humira, respectively (Centocor's license was part of a litigation settlement between Centocor and Serono). Terms are not public. However, Centocor does not pay royalties on sales, while Knoll does (Rader, 2006). My impression from comparing US patents issued to Yeda Research and Development (Weizmann's technology commercialization arm) and Peptech is that the latter's patent coverage of TNF antibody technology is more extensive than the former's.

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