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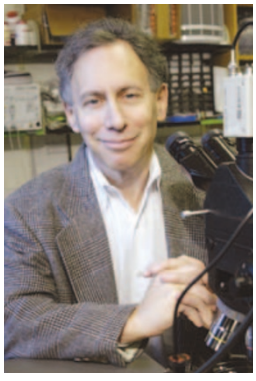


ON THE COUCH
Type 2 diabetes
Drugs in late-stage pipeline will broaden therapeutic options (p 367).

Third Tysabri adverse case hits drug class

Theoretical concerns about drug ring true but many questions remain unanswered.

Cormac Sheridan

The future of several drugs for autoimmune disorders hangs in the balance after a third case of a rare neurological disorder was detected in patients taking the monoclonal antibody natalizumab (Tysabri; Biogen Idec/Elan).

Biogen Idec and Elan suspended sales of Tysabri in February after one patient died of progressive multifocal leukoencephalopathy (PML) during a clinical trial of Tysabri in combination with interferon β-1a (Avonex; Biogen Idec) for multiple sclerosis. A second patient was later confirmed as having PML.

It wasn't clear whether the adverse effects arose from Tysabri alone, or in combination with Avonex. The third case arose in a trial with Tysabri alone for Crohn's disease. A patient, who died in December 2003, had been diagnosed with a form of brain cancer called malignant astrocytoma. This diagnosis was changed after the companies' re-evaluated the medical file.

But it was disclosed that the third Tysabri patient with PML had taken azathioprine for five years, an immunosuppressant drug that has been linked with PML. And positive two-year trial data recently presented at a meeting of the American Academy of Neurology in Miami complicates the matter. In 942 patients Tysabri reduced the risk of greater disability by 42% compared with a placebo and reduced the rate of clinical relapses by 67%.

Biogen and Elan are trying to establish Tysabri's risk/benefit profile by scouring data from around 3,000 clinical trial patients. But in the meantime, similar drugs in development have suffered in Tysabri's wake. The FDA put a hold on Phase IIb clinical trials of GlaxoSmithKline's experimental small-molecule drug for multiple sclerosis, called 683-699, because it is in the same drug class as Tysabri —known as α4 integrin antagonists. An Australian biotechnology company, Antisense Therapeutics, has voluntarily halted Phase IIa trials on ATL1102, its antisense therapeutic that targets α4 integrin.

The cause of the problem could be that Tysabri does its job too well. Tysabri is thought to work by preventing T cells that trigger the autoimmune reaction in multiple sclerosis from crossing the blood–brain barrier, entering the central nervous system and attacking the myelin sheath that insulates nerve axons.

Tysabri does this by preventing the formation of an adhesion complex on the surface of T cells. Different combinations of integrins in the complex were thought to act as tissue-specific 'zip codes', which enable immune cells to home in on particular tissues.

Now it is known that the α4 integrin homes in on a range of organs in other autoimmune diseases, which explains the apparent efficacy of Tysabri in conditions such as Crohn's disease and rheumatoid arthritis. However, this wider suppression of T-cell function raised fears that these treatments could weaken patients' ability to fight other infections.

"I'd been worried for years that this therapy had the potential risk to lead to opportunistic infections."

For years, Lawrence Steinman has warned of potential side effects in Tysabri and related drugs.
STANFORD UNIVERSITY

"I'd been worried for years that this therapy had the potential risk of leading to opportunistic infections," says Lawrence Steinman, Professor of Neurology at Stanford University, California, and one of the co-authors of the original paper that described Tysabri's action (Yednock, T. *et al. Nature* 356, 63–66 (1992)).

One-year data from the AFFIRM and SENTINEL Phase III trials — which evaluated Tysabri as a monotherapy and in combination with Avonex, respectively — showed no major difference in levels of opportunistic infections between treatment and controls, according to the FDA ▶

label for Tysabri. But data published last year by a group at the Beth Israel Deaconess Medical Center, at Harvard Medical School provide indirect evidence that compromised immune surveillance systems could lead to PML (Du Pasquier, R. A. *et al. J. Virol.* 78, 10206–10210 (2004)).

PML, a demyelinating disease of the central nervous system, is most often seen in immunocompromised patients. It is associated with the activation of JC virus (JCV), a human polyoma virus that is normally latent in more than 80% of healthy individuals.

"If immune surveillance was generally compromised, why have only PML cases been observed?"

Igor Koralnik and colleagues detected cytotoxic T lymphocytes specific to JCV in 8 out of 11 healthy volunteers, suggesting that these T cells help to keep JCV at bay. Tysabri, therefore, could be preventing these protective T cells from crossing the blood-brain barrier and carrying out their protective role.

What isn't clear is how JCV, which is found latent mainly in the kidney, travels to the brain to wreak its destruction. "The question is where the actual site of latency is in these patients," says Koralnik, Associate Professor of Neurology at Harvard Medical School.

But if immune surveillance was generally compromised, why have only PML cases been observed? Other opportunistic infections, such as tuberculosis and herpes, would be expected, says Steinman. One possibility is that JCV might have some unique features that enable it to mount an attack. The lack of evidence of such cases so far is "interesting and unexplained," he says.

Definitive evidence for whether the adverse effects arose from Tysabri alone, or in combination with Avonex, will rest entirely on epidemiological analysis of the different trial groups, says Steinman. But with patient numbers of around 1,000 in each trial, providing firm evidence could be tricky. "It is difficult to make ironclad conclusions when the database is so limited," says Steinman.

Mergers in Japan help firms retain own products

Newly formed companies have more financial clout to compete with Western companies.

Ichiko Fuyuno

The merger of two of Japan's biggest pharmaceutical companies is the latest in a string of merger and acquisition activity designed to free firms from foreign involvement with their products.

Sankyo and Daiichi Pharmaceutical announced a merger in February to maintain Sankyo's position as the country's second-largest drug company behind Takeda Pharmaceutical. In April, Yamanouchi Pharmaceutical and Fujisawa Pharmaceutical will complete its merger to become Astellas Pharma, keeping Yamanouchi in third position. A merger between Dainippon Pharmaceutical and Sumitomo Pharmaceuticals is set for October.

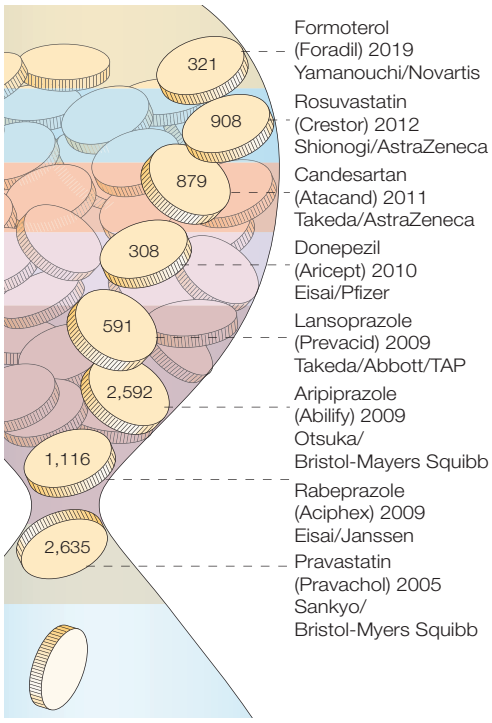
Behind this domestic activity lies growing fears about upcoming legislation revisions, expected to take effect in 2007. The changes will make it easier for foreign companies to acquire Japanese firms by allowing them to be purchased using stock swaps. Japanese pharmaceutical companies would be particularly ripe for takeover because they have not grown in tandem with Western companies over the years, despite the country having the second largest drug market worldwide.

A lack of overseas sales channels and small R&D budgets have seen companies miss out on a chunk of profits from several blockbuster drugs, such as pravastatin (Pravachol) and Lansoprazole (Prevacid), that were discovered in Japan (see FIGURE). According to Robert Kneller, Professor at the Research Center for Advanced Science and Technology at the University of Tokyo, of the 16 Japan-origin drugs approved by the US FDA in 1998–2003, at least 8 were licensed out to US and European companies (*Nature Biotechnol.* 23, in press, June 2005).

With looming patent expiries on many major products placing further pressure on Japanese companies, firms are adopting strategies that maximize profits from their own discoveries. "One reason we chose to merge is that we want to create a global cycle of selling by ourselves, recovering profits by ourselves and using the funds for our R&D," says Shin Ohkubo, a spokesman at Yamanouchi.

Yamanouchi made a great leap in January when, for the first time, it sold a drug — solifenacin succinate (Vesicare), a muscarinic receptor antagonist for overactive bladder — through its own sales network in the all-important $248-billion US market.

Analysts say there are several promising drugs of Japanese origin under development, such as Sankyo's acyl-coenzyme A cholesterol acyl-transferase (ACAT) inhibitor CS-505 for atherosclerosis, which is now in Phase II trials in the US. It is thought that the treatment could earn upwards of $2.8 billion worldwide.



Patent expiries on top-selling drugs are forcing Japanese companies to change their business models (2004 sales in US$ millions).

Japan's biggest company, Takeda, plans to increase its US salesforce by about 500 to ~1,800 when its potential blockbuster treatment for insomnia, TAK-375, is due to be approved by the FDA in 2006. It currently only markets the antidiabetic treatment pioglitazone (Actos) through its own sales channel in the US.

Consolidation would also make companies cope better with the high costs of drug development. It is thought that Japanese companies need to allocate around $955 million for R&D to compete effectively with US firms. The figure is dwarfed by Pfizer's $7.1-billion R&D expenditure, but Sankyo currently spends about $820 million, whereas Daiichi spends almost $560 million.

Mitsuo Ohmi, an independent pharmaceutical analyst in Tokyo, says Japanese companies are even thinking of acquiring small foreign companies. In February, Takeda announced a plan to buy Syrrx, a California-based biotechnology company specializing in high-throughput X-ray crystallography technologies. All the other major Japanese players — Astellas, the planned Daiichi/Sankyo and Eisai — see overseas M&A as an option to grow further, Ohmi says.

FDA pharmacogenomics guidance sends clear message to industry

Pharmacogenomic information will be an essential element in drug submissions.

Mark Ratner

After much anticipation, the US Food and Drug Administration delivered its final guidance document on Pharmacogenomic Data Submissions on 22 March.

Companies have eagerly awaited the document since the original mid-2004 release date to see how the agency will interpret the complexities surrounding the use of pharmacogenomics or pharmacogenetics test in conjunction with drug therapy.

But rather than criticizing FDA for delay, the pharmaceutical industry is praising the initiative. "If this had been a watered-down version of the draft guidelines, we'd be saying this is not a clear path, that it'll take longer to be adopted and supported by FDA," says Kevin Rakin, CEO of Genaissance Pharmaceuticals.

These guidelines will encourage the pharmaceutical industry to take pharmacogenomics more seriously, says Jürgen Drews, former president of R&D at Hoffmann-LaRoche. "So far, it was an option that took time and money, but with no obvious reward to it." Fearing that pharmacogenomic data would affect drug approvals, many companies have not submitted such data to FDA or avoided research in this area.

The Guidance describes what data will be needed during the review of marketing applications, the format for submissions and the data that will be used during regulatory decision making. In shaping the guidelines, FDA took the bold step of having peer-to-peer scientific discussions with companies. "FDA has never had informal meetings with industry in the past," says Lawrence Lesko, FDA's director of the Office of Clinical Pharmacology and Biopharmaceutics.

Part of the delay in releasing the final document stemmed from the need for separate reviews at the centres for the evaluation of drugs, biologicals and devices. "That was an unusual step for us," says Lesko. "But pharmacogenomics is intertwined into the business of all them."

Another problem was the amount and quality of test data voluntarily submitted by companies to help develop the guidelines. "FDA went in thinking there would be a large amount of data with real products, but the submission rate has been slower," says Allen Roses, Senior Vice President, Genetics Research, at GlaxoSmithKline. FDA has had ten formal submissions and meetings with companies, according to Lesko, and much of the data are difficult to interpret. "That's not a surprise," he says.

The agency is keen to receive and learn from more exploratory data, and the Guidance explains that any so-called Voluntary Genomic Data Submission (VGDS) of research data will be reviewed purely to help FDA and industry gain experience in developing and handling pharmacogenomic data. Wyeth says it has learnt a lot from its two VGDS submissions. "We got a better feel for how [FDA] would like to see data extracted from clinical databases," says Andrew Dorner, Senior Director, Translational Research at Wyeth Research. "It's coloured how we complete the design of our systems for data processing and analysis."

The guidance also addresses another of industry's concerns by setting criteria for which genomic tests are valid biomarkers (see BOX). Those details, along with fuller description of the operating procedures companies can follow, "will give industry confidence — seeing them in black and white", says Chris Webster, Director, Regulatory Strategy and Intelligence for Millennium Pharmaceuticals.

However, differences remain around the eagerness of companies to use the process. Plus, although many large drug companies have strong internal pharmacogenomics groups, mid-sized companies, which have good drugs and a more local clientele, usually do not have extensive knowledge and resources in this area, says Drews. "However, with the biotech companies, they can probably become the motor of propagating pharmacogenomics standards."

Releasing the Guidance should change that thinking. "FDA doesn't spend its resources, which are in constant stress in a variety of directions, to work hard and issue this kind of document unless they see it as the future," suggests Samuel Broder, Chief Medical Officer at Celera Genomics.

"FDA has now made it clear that as the technology base grows, it will move toward stricter regulatory rules," says Drews. The decision by FDA to publish "is a definitive step in favour of the progressive forces in industry and biotech."

BIOMARKER DEFINITIONS

Valid biomarker. A biomarker that is measured in an analytical test system with well-established performance characteristics.
Known valid biomarker. Widespread agreement in the medical or scientific community about the physiological, toxicological, pharmacological and/or clinical significance of the results.
Probable valid biomarker. A scientific framework or body of evidence that seems to elucidate the physiological, toxicological, pharmacological and/or clinical significance of the test results. Is not classified as a known valid marker for any one of the following reasons:
- Data revealing its significance might be a company's proprietary knowledge and might not be available for public scientific scrutiny.
- Data revealing its significance, although highly suggestive, might not be conclusive.
- Independent verification of the results might not have been obtained.

Source: FDA

NEWS IN BRIEF

Bextra withdrawn from market

The US and European regulatory authorities have asked Pfizer to withdraw its selective cyclooxygenase 2 (COX2) inhibitor, valdecoxib (Bextra), from the market.

The lowdown. Is this a sign that the FDA is becoming more cautious, after facing pressure over its handling of drug-safety issues? The FDA's decision went against the advisory committee's narrow vote in favour of keeping Bextra on the market — although the committee didn't take into account Bextra's other adverse effect of allergic skin reactions. Unlike the EMEA, the FDA called for black-box warnings of cardiovascular and gastrointestinal risks to appear on all prescription versions of non-steroidal anti-inflammatory drugs, and strong warnings to appear on over-the-counter painkillers, despite no strong evidence for a risk. Ironically, the FDA's decision could be beneficial for Pfizer. Its celecoxib (Celebrex) is now the only selective COX2 inhibitor on the market and so could re-establish a large proportion of its sales, which reached $3.3 billion last year. Celebrex could also pick up a portion of Bextra's revenues, which made $1.29 billion in sales last year.

More success for Avastin

An interim analysis of a Phase III study in metastatic breast cancer has shown that bevacizumab (Avastin; Genentech) plus paclitaxel (Taxol) improves progression-free survival by an average of 4 months compared with chemotherapy alone.

The lowdown. The results from the breast cancer trial, which was sponsored by the US National Cancer Institute, come as a slight surprise. Avastin had previously failed in a breast cancer trial in combination with capecitabine, but researchers think that this was because the trial looked at people with advanced disease rather than metastatic breast cancer. Although the analysis of safety data is not complete, analysts are already saying that the results could make Avastin the biggest-selling cancer treatment. Avastin is approved for colorectal cancer, and a recent trial showed that the drug also prolonged the lives of patients with lung cancer. According to conservative estimates, annual revenues would pass $3 billion if Avastin is prescribed for all three indications.

Novel Indian generics agreement

Dr Reddy's Laboratories has entered into a $56-million agreement with ICICI Venture Funds Management Co. for the development and commercialization of Abbreviated New Drug Applications.

The lowdown. Dr Reddy's has been looking for a financial suitor for months. R&D spending reaching around 15%, increasing competition in the US generics market, no big product launch for 2 years and litigation costs from patent challenges have all been eating into profits. The new funding model is aimed at boosting Dr Reddy's penetration of the US generics drugs market while easing its R&D cost burden. ICICI, a private equity and venture capital fund, will fund the development, registration and legal costs related to the applications for marketing around 30 generics during the fiscal years 2004/2005 and 2005/2006. ICICI will provide $22.5 million in the first phase and $33.5 million in the second phase.

HPV vaccine effective

A Phase II study has shown that the vaccine Gardasil reduces the incidence of infections that lead to genital warts and cervical cancer by 90%, according to a paper in the *Lancet Oncology* (doi:10.1016/S1470-2045(05)70101-7).

The lowdown. The findings provide some good news for Merck, which is racing against GlaxoSmithKline to bring a cervical cancer vaccine to market. Merck plans to file Gardasil for regulatory approval with the FDA in the second half of 2005, and GSK expects to file its rival vaccine, Cervarix, for approval in Europe in 2006. Gardasil protects against two strains of the human papillomavirus (HPV) responsible for cervical cancer and two responsible for genital warts, whereas GSK's Cervarix targets just cervical-cancer-related strains. Success will not just be based on efficacy and being first to the post. Although Gardasil has the added plus for public health of offering protection against genital warts, which can cause sexual dysfunction, promoting a vaccine that protects against sexually transmitted disease to parents of young girls could be tricky.

Partnership to develop TB drugs

The Global Alliance for TB Drug Development and GlaxoSmithKline are to collaborate on a joint drug discovery programme to develop treatments for tuberculosis.

The lowdown. To tackle the fact that there have been no new TB drugs introduced for more than 40 years, the public–private partnership will work on four projects that will target the TB-causing bacterium *Mycobacterium tuberculosis* at GSK's research laboratories in Tres Cantos, Spain. One project will work on optimizing a

WORLD HEALTH ORGANISATION

novel class of antibiotics called pleuromutilins, and two target-based projects will work on the enzymes isocitrate lyase and InhA. The fourth project will screen GSK's antimicrobial libraries for novel compounds that have the ability to kill *M. tuberculosis*. The TB Alliance and GSK will support 25 full-time scientists each, and GSK will absorb overhead costs. One precondition of the partnership is that any resulting drugs are sold at low prices in developing countries.

Cuts announced at Pfizer

At an analysts and investors meeting, Pfizer said it will be cutting annual costs by $4 billion, or 12%, by 2008 to help keep its profits rising.

The lowdown. The level of cost-cuts is twice as much as some analysts had expected. Growth this year will be low, affected by the patent expiration of gabapentin (Neurontin) last year and plummeting sales of celecoxib (Celebrex) and valdecoxib (Bextra) — this announcement was made the day before FDA's decision on Bextra. Facing patent expiries on Zoloft, Zyrtec and Norvasc, Pfizer could lose as much as $9 billion in revenue in the next 4 years. Investors reacted well to Pfizer's plans, but some analysts remained unconvinced, as Pfizer did not disclose details of how the cost-cutting would be achieved. Without such details, wrote Prudential Equity Group analyst Tim Anderson in a note to investors, it will be difficult to tell whether the company is meeting its stated goals, except by watching the bottom line.

Study questions effectiveness of Alzheimer's drug

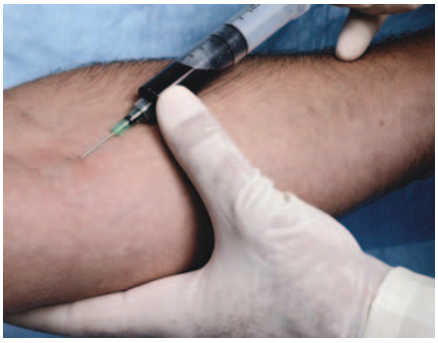
A study in the *New England Journal of Medicine* reports that any effect of the cholinesterase inhibitor donepezil (Aricept; Pfizer) in Alzheimer's disease wears off after 3 years. (Petersen, R. C. *et al. NEJM* 13 April 2005 (doi:10.1056/NEJMoa050151)).

The lowdown. The findings suggest any benefits from Aricept in slowing the rate of progression of Alzheimer's disease in patients with mild cognitive impairment are limited to the first 12 months of treatment. Most of the benefit seen with Aricept occurred among people with the *APOE*E4* gene variant, which has been linked to an increased risk of Alzheimer's. The implications for Aricept's future are unclear. According to an accompanying editorial by Deborah Blacker from the Harvard Medical School, Aricept "may offer some benefit, but any such benefit is quite limited and apparently transient." A more clear-cut result from the trial was that the widely used antioxidant vitamin E does not prevent Alzheimer's despite its use as an early intervention for mild cognitive impairment.

Sanofi wins Plavix patent case

The Canadian Federal Court of Ottawa has granted Sanofi-Aventis's request to block a challenge by Apotex against its patent for clopidogrel (Plavix).

The lowdown. Sanofi-Aventis has won the first of several cases against generics companies contesting patents on its top-selling drug. The lawsuits centre on claims that the patent on Plavix is invalid because it has already been described in an expired patent. Plavix was originally a racemic mixture and the patent on the racemic mixture expired in 2003. But the patent covering the enantiomeric drug is valid until 2011. The trial verdict was under doubt because many analysts thought that Sanofi's takeover bid for Aventis in 2004 signified a lack of confidence in the result. But the positive outcome for Sanofi in Canada suggests that it could also win the pending cases against Apotex and Dr Reddy's Laboratories in the more lucrative US market.



Success for nonprofit pharmaceutical company

The Institute for OneWorld Health, the first non-profit pharmaceutical company in the US, has shown that their unique R&D approach to tackling diseases of the developing world could work. The organization hunts for drugs that have stalled in development, asks their owners to donate the intellectual property if the compound is still under patent, raises development funding from non-commercial sources and utilizes the scientific and manufacturing capacity of the developing world. In this case, the Institute took on the role of developing an injectable form of paromomycin as a treatment for visceral leishmaniasis after the World Health Organization was unable to find a sponsor for a large-scale trial. At the 3rd International Congress on Leishmaniasis in Palermo, Sicily, researchers presented data from a trial showing that paromomycin worked as well as the standard treatment, amphotericin B, which costs more than 10 times more for a course of treatment. The Institute has received a grant of nearly $10 million from the Bill & Melinda Gates Foundation to continue advancing paromomycin through the approval and post-approval process in India this year.

NEWS FEATURE

ARGENDIA

An array of problems

Despite the huge amount of published microarray data in cancer, little is being converted into clinical practice. Validating initial data is proving to be a key challenge, reports SIMON FRANTZ.

Like many researchers in their field, Serge Koscielny and Catherine Hill wanted to use microarrays to uncover clues to cancer prognosis. With the ability to track the expression of thousands of genes that might be switched on or off in tumours, it's no surprise that microarrays are being increasingly used to generate molecular profile maps that identify subgroups of patients who have a high-risk cancer, or who could respond well to oncology treatments.

But their initial attempts to generate reproducible data proved frustrating. In such studies, patients are often separated into a so-called training group, which identifies possible gene-expression patterns that are characteristic of people at high-risk of aggressive forms of colorectal cancer, for example, and a validation group, which independently confirms the molecular signature from the training group.

To the surprise of Koscielny and Hill, their efforts stalled at the training group stage. Different sets of patients kept giving different results. "We decided to see if the same situation occurred in the data from other published papers," says Koscielny, from the Biostatistics and Epidemiology Unit at the Institut Gustave Roussy, Villejuif, France.

Koscielny, Hill and their colleague Stefan Michiels repeated their experiments on publicly available data sets from seven of the largest cancer microarray studies published on cancer prognosis. Even with published results, they couldn't reproduce most of the data[1]. As stated in an editorial accompanying their study, published in *The Lancet*, five out of the seven studies were no better at predicting patient subgroups than tossing a coin[2].

Beyond the hype

Concerns about the reproducibility of cancer microarray data come at a time when the field is beginning to ask why the huge amount of profile data in the literature is not being converted into clinical practice. "Everyone is enthusiastic about the technology, but most people realize that there is a problem," says John Ioannidis, from the Department of Hygiene and Epidemiology at the University of Ioannina, Greece, and author of the editorial that commented on the study.

The difficulty is that in contrast to most past microarray experiments, which looked at carefully controlled experimental systems, these studies are blindly examining the complexity of human tissues and cancer. This essentially makes most of these experiments both hypothesis-generating and hypothesis-validating at the same time. "The challenge is to do effective exploration while people are feeling their way through," says David Ransohoff, Professor of Medicine and Epidemiology at the University of North Carolina in Chapel Hill, USA. "The *Lancet* articles present a critical challenge to important published papers by suggesting that validation was not independent as authors seemed to suggest, so that chance may explain results."

> Everyone is enthusiastic about the technology, but most people realize that there is a problem.
>
> JOHN IOANNIDIS, UNIVERSITY OF IOANNINA, GREECE

Most researchers agree that the random signals or 'noise' generated in these data do not reflect lack of robustness or stability of the technology platforms used, but have a more fundamental source. "There's not a robust understanding of what it takes to validate a biomarker," says James Jacobson, Chief at the National Cancer Institute's Cancer Diagnosis Program.

"A lot of this profiling data will not be replicated, as you're seeing papers published on relatively small test sets that are not as clean when taken out into a larger, more diffuse, set of patients or samples," says Nic Dracopoli from Bristol-Myers Squibb. "These are still relatively early days, but what the community needs to do is to be more rigorous about what we're doing and publishing."

Like any technology in its infancy, the high costs of individual experiments means that most

> You cannot begin to comprehend what a world of difference it is to run a research microarray lab as opposed to a clinical diagnostic lab.
> RENE BERNARDS, NETHERLANDS CANCER INSTITUTE

researchers will carry out small studies. Early cancer microarray studies typically looked at tens of patients, making validating data difficult. "If you're looking at the expression of around 20,000 genes in this number of patients there is an enormous amount of noise," says Hill.

Truly independent?

Increasing sample sizes to hundreds of patients, and verifying early data in larger independent groups, should provide greater confidence in the robustness of the molecular profiles obtained. But the *Lancet* paper shows that even if the data seem to be reproducible, they might not be providing the correct kind of information.

Reporting the best results in gene expression creates highly selective results, and this reduces the likelihood that they will be replicated. "We found that the list of genes that are most differentially expressed in the populations studied varied greatly," says Hill.

"The *Lancet* paper suggests that there must be some selection in the process of finding and validating these markers," says Ioannidis. "Something was selected because it looked too good."

Ioannidis suggests that one way of solving this is to test data truly independently. "We see lots of papers in high-quality journals with independent validation of the data done by practically the same team, or the same consortium, and this is not fully independent," he says. "I would even like a different team to see if the findings stand the test."

Part of the problem in reaching a consensus about what should be done seems to be a culture clash between the molecular biologists, technology researchers and the clinical disciplines involved in developing these microarray tests. "When these groups don't talk well together, you get design problems that lead to results that we can't trust," says Ransohoff.

There should be more communication with epidemiologists who are well versed with the issues being faced in observational or non-experimental research, says Ransohoff. "The basic rules of evidence for understanding whether observational studies such as those producing microarray data are reproducible and reliable are well evolved in clinical epidemiology," he says.

Linking academia, industry, government and technology together through directed medium-focus science projects would promote interactions and provide insights needed to help large-focus science efforts, says Stephen Friend from Merck. "As work gains momentum I think the gap between published profiles and the clinic will be closed by these medium-focused projects," he says.

Complete validation

Solving these issues is crucial, because ultimate verification of these data can only come from the prospective validation of an independent group in a clinical trial, and this is not a trivial or inexpensive task.

> What the community needs to do is to be more rigorous about what we're doing and publishing.
> NIC DRACOPOLI, BRISTOL-MYERS SQUIBB

Rene Bernards and Laura van't Veer from the Netherlands Cancer Institute are running the first prospective trial for a microarray test in cancer. The test, called MammaPrint (one of the few that did pass the test of the *Lancet* publication), measures the expression profile of 70 genes that are predictive of the risk of metastasis in breast cancer[3]. The gene set was co-developed with Rosetta Inpharmatics/Merck and this test has been developed by a company called Agendia. A trial called MINDACT, started with a pilot last month, will ultimately enrol 6,000 breast cancer patients to compare both classical diagnostics and MammaPrint in assessing risk.

Although getting to this stage has taken just 2 years from the initial publication, it has involved extensive testing. The profile had to be verified both in a further study[4], and by an independent consortium called TRANSBIG, because the overlap between the original training and validation group raised queries about the validity of the data.

Developing the test is also no easy task. "You cannot begin to comprehend what a world of difference it is to run a research microarray lab as opposed to a clinical diagnostic lab," says Bernards. Standard operating procedures need to be established and everything needs to be quality controlled, from the isolation of RNA to the bioinformatics set up. "As there are no clinical labs worldwide that are performing microarray analyses you have to write the book as you go along," says Bernards.

Then there is the matter of costs. "Retrospective validation is expensive; prospective validation is nearly unaffordable," says Bernards. Agendia's arm of the MINDACT trial will cost in the range of €10 million and take 6 years to complete. Such costs will be impossible to recoup but are necessary if microarrays are to gain acceptance in the medical community as a diagnostic tool. "Once people see that validation can be obtained in a prospective trial it will be easier for other tests to gain acceptance, and we have also learnt a lot more about the logistics of collecting tissue samples from large numbers of clinical centres," says Bernards.

The complexity of the technology and quality control involved in the development of MammaPrint means that the test will be carried out in a single centralized laboratory for the near future. But a group centred around the National Cancer Institute are trying to go one step further by verifying signatures from three papers by multiple laboratories that have predicted a group with a better prognosis in very early-stage lung adenocarcinoma[5–7]. As a prelude to a larger confirmation study in lung cancer patients, the group recently showed that the data generated can be consistent between several labs[8].

Research groups are only just beginning to do the hard work of confirming and validating studies, but with greater consideration of design and appreciation of all the potential confounding issues, the leap from published data to the clinic stands a greater chance of success. "People just have to be a lot more careful — there's a growing sophistication in the statistical community about how to handle these data," says Jacobson. "There needs to be a lot more care taken in the way the data are actually handled and the claims that are made in publications."

1. Michiels, S. *et al. Lancet* **365**, 488–492 (2005).
2. Ioannidis, J. P. A. *Lancet* **365**, 454–455 (2005).
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PATENTWATCH

Traditional knowledge counts as prior art

After a 10-year battle, the European Patent Office (EPO) has revoked a patent on a fungicide made from seeds of the Neem tree, which is indigenous to the Indian subcontinent, on the grounds of novelty. The decision is seen as a victory for campaigners fighting to stop companies exploiting plant products at the expense of people in the developing world.

The patent (EP436257), jointly owned by global company W. R. Grace and the US Department of Agriculture, was granted in 1994 for Neem-based biopesticides for use on food crops. After the patent was granted, the Indian environmentalist Vandana Shiva, Magda Aelvoet (now Belgian Minister of State) and the International Federation of Organic Agriculture Movements mounted a legal challenge. They claimed that the fungicidal properties of the Neem tree had been broad public knowledge in India for many centuries, both in Ayurvedic medicine and in traditional agricultural practice. The patent therefore lacked the basic statutory requirements of novelty and inventive step, they argued.

They also charged that the patent was contrary to morality, because the patent holders were, in essence, stealing a method that is part of the traditional knowledge base of India. But in 2000, the Opposition Division determined that the patent was not contrary to morality as stated by the European Patent Convention.

India bill leaves generics breathing space

Several last-minute amendments to India's new patent bill mean that its impact will not be as restrictive for domestic generic manufacturers as was anticipated by some commentators.

The bill is a requirement of the World Trade Organization's Trade Related Intellectual Property (TRIP) agreement that India signed in 1995. Drugs discovered before 1 January 1995 are therefore unaffected by the new legislation. Patents can be awarded to drugs that have been discovered between 1 January 1995 and

1 January 2005, but only if patents for these drugs were filed by the latter date. Processing of these ~9,000 patent applications only started at the beginning of 2005 and is expected to take several years to complete, so generics manufacturers can continue to freely make copies of these drugs until the point the patent is issued.

Patent protection will last 20 years from the date of filing and not from the date of award. Responding to criticism that the new bill will deprive the developing world of cheaper generics drugs, the Indian government said the new law applies to only 10 of the 195 drugs currently on sale in India (such as tenofovir, emtricitabine and atazanavir), and that 97% of all the drugs sold in India are off-patent.

Perhaps the biggest change in legislation, and the one of most interest to multinational drug companies, concerns the ability to patent any new drug discovered after

1 January 2005. These drugs will be afforded full 20-year patent protection, but with some qualifications. The drug must not have been published or used anywhere in the world before the patent application, and Indian companies can contest the awarding of patents on various grounds.

Even when a patent is issued, generics companies could still manufacture copies under a compulsory license granted by the government to enable the use of patented material, but they will have to pay royalties to the patent holder. The government could also step in to allow the copying of drugs in medical emergencies, or if it deemed drug prices to be excessively high.

Patent holders will also have to demonstrate genuinely 'inventive steps' if they want to renew their patents, rather than claiming new uses for old drugs. This move is intended to stop the so-called 'evergreening' process, in which a company acquires patents on several different properties or uses of the same drug.

Despite these conditions, the new laws will finally grant Western pharmaceutical makers access to both the Indian market and the manufacturing expertise built up by the US$5-billion Indian drug industry. The rise of domestic companies was built around 'process patents', in which generic versions of patented drugs were allowed if they were produced by a slightly different method of synthesis — essentially allowing the reverse engineering of branded pharmaceuticals. Many multinational companies are reportedly already striking deals with smaller Indian firms to take advantage of this expertise in low-cost drug manufacture, as well as the convenience of having an English-speaking workforce.

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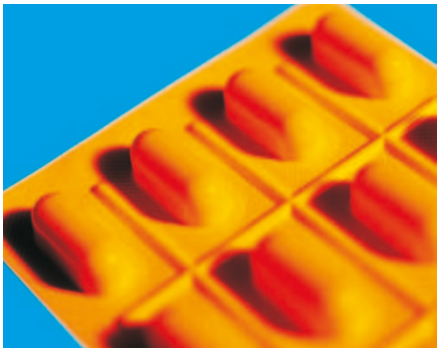

PATENT PRIMER

Interferences: rights of the first inventor in the US

Laurie L. Hill

What happens if someone else claims to have invented your invention? In the United States, only the first inventor has rights to patent protection of an invention. When two or more parties claim to have invented the same invention, an interference determines the actual first inventor, who will subsequently be awarded the patent rights.

The rights of the first inventor are unique to US patent law. Most other jurisdictions, including Europe, Canada and Japan, award the patent rights to the inventor who first files a patent application. The 'first to file' jurisdictions consider the diligence of the first filing inventor most deserving of patent protection, whereas US patent policy recognizes the individual's right to their creation. In all jurisdictions, the application must be filed on the behalf of an actual inventor, because a party who simply derives or steals an invention from someone else cannot obtain patent rights. These underlying policies shape the legal rules and procedures for interferences.

Triggering an interference

The examiner of a pending patent application has the discretion to declare an interference to determine who invented the claimed invention first — that is, the priority of invention — on his or her own initiative or at the suggestion of an applicant. An interference can be declared between two or more pending applications or an issued patent and one or more pending applications that claim the same (or substantially the same) invention. An examiner determines whether the same invention is claimed using the two-way patentability test. Simply stated, if invention A anticipates or renders obvious invention B, and vice versa, the examiner can declare an 'interference in fact'. Once the examiner determines that the same invention is claimed and can be patented by each party, the examiner defines the subject of the interference using one or more hypothetical claims or 'counts'.

Once triggered, interferences are procedurally complex, resembling a mini-trial with motions and discovery that culminates in a hearing before an administrative trial judge. The interference focuses on a factual determination of the priority of invention as well as some patentability issues.

Conception and reduction to practice

A party establishes priority of inventorship by showing that he or she first made the invention or first conceived of the invention and exercise reasonable diligence in later making it.

Conception of an invention lies in the mental construction of a complete and operative invention. The party must show possession of every invention feature and prove by corroborating evidence that the party disclosed the invention to others in such a way that someone else in the field could make and use it. Such evidence can include notebook entries and sufficiently detailed models that fully convey the invention. Corroboration of conception requires something more than the inventor's testimony. The strongest evidence is typically a complete and detailed description of the invention signed by a disinterested third party.

Reduction to practice looks to when an operative invention was actually made. The filing of a patent application itself can serve as a 'constructive' reduction to practice if certain patentability requirements are met. Alternatively, an inventor establishes reduction to practice by demonstrating the actual making of an operative embodiment of the invention. Definitive reduction to practice can be complicated for biotechnological inventions because of the testing associated with determining whether or when a biological invention is actually able to perform as claimed. For example, in some cancer therapy inventions, a patent application contains only *in vitro* and animal study data. Yet, a method of treating a patient requires clinical studies to demonstrate efficacy that usually occur years after the application is filed. In such cases, reduction to practice relies on the subjective strength of the preclinical data supporting the claimed invention.

In a nuance peculiar to biotechnological inventions, conception of certain inventions are not recognized in US patent law without a simultaneous reduction to practice. For example, conception of novel DNA sequences and new chemical compounds can necessitate the disclosure of a definitive structure, name or formula, or definitive chemical or physical properties — an effective reduction to practice — in order to prove conception.

Winning the interference

If an inventor demonstrates the earliest conception and reduction to practice, he or she will prevail in an interference. If, however, an inventor has the earliest date of conception but reduces the invention to practice after the second inventor, a more complicated analysis ensues. The inventor with the earliest conception date also must show a reasonable diligence — that is, consistent efforts — towards making the invention from the date of conception forward. If the inventor demonstrates such efforts, then the inventor with the earliest conception date prevails. However, if the first inventor abandons, suppresses or conceals the invention rather than exercising reasonable diligence in reducing it to practice, the second inventor can be granted priority and the associated patent rights.

STRATEGIC BUSINESS CONSIDERATIONS

The primary consideration in any patent decision should be whether your overall strategic and business goals benefit from investing resources into patenting efforts. This is particularly true of an interference, a proceeding that is usually expensive and time-consuming. So, here are a few questions to consider:

- **Is there an easier way to obtain the necessary patent protection? Sometimes amending the claims to avoid the interference while retaining protection of the commercially valuable invention might be an option.**
- **What is the expected benefit from winning the interference? The cost of an interference in time and resources can significantly outweigh the expected benefit of winning. On the other hand, if a successful interference knocks out a dominating patent in a sector in which you will be selling your product, the time and money might be worth it.**
- **Can you afford a significant delay in obtaining patent protection? In extreme cases, the resolution of an interference can take up to 10 years. Markets for products rarely lay fallow for such long periods. You should therefore consider whether your invention is one that will still provide adequate return if the interference process lasts for several years.**

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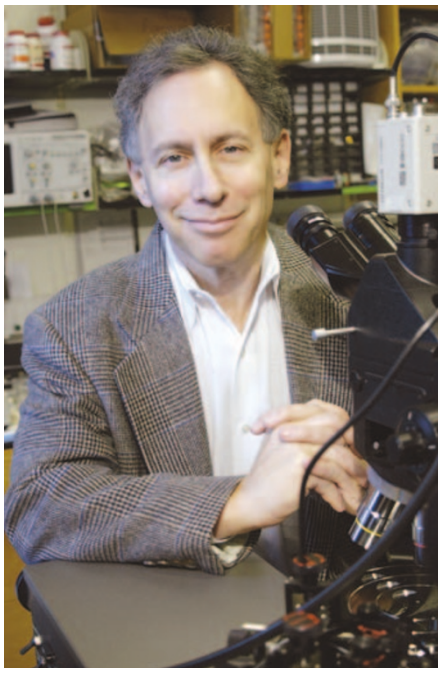
CAREER PATH

Robert Langer



Robert Langer was recently named Institute Professor at the Massachusetts Institute of Technology (MIT), the highest accolade awarded by the MIT faculty, and has been cited by MIT colleagues and others as "an extraordinary scientist" and "one of history's most prolific inventors in medicine." Despite having worked in academia for all of his career, Langer evidently has his foot in the industry camp too: his collaborative and innovative approach to inventing and developing medical devices has led to more than 500 issued and pending patents, many of which have been licensed to pharmaceutical and biotechnology companies worldwide. As a chemical engineer working in biology, his success is a great example of how taking an unconventional career path can be both fruitful and rewarding.

Langer's career has seen him honoured with many awards. He is a recipient of the Draper Award, the engineering equivalent of a Nobel prize, and very recently has been awarded the largest US medical prize, the Albany Medical Center Prize, and is to share the 2005 Dan David Prize for Materials Science. But the Institute Professorship has particular resonance after what he admits was a "rocky start" at MIT. Indeed, his career could have been a very different story if he'd taken the advice of some MIT colleagues early on when initially trying to apply engineering principles to solve biological problems.

"Some professors felt I didn't fit in, and some of my fellow researchers thought my work was unimportant and even suggested that I should leave." It's an experience that has left Langer keen to encourage his own students to believe in themselves and stretch themselves scientifically, whether it be taking on a new, challenging discipline or turning their back on the obvious career path.

Langer graduated in 1974, but unlike many of his peers who took the obvious route into the oil industry, the prospect of such a career did little to entice him. Instead, he wanted his work to benefit human health, and so for his postdoctoral studies he joined the laboratory of Judah Folkman, renowned cancer researcher and pioneer of the drug delivery implant, Norplant, at Boston's Children's Hospital. It was a wonderful opportunity for Langer: "It was my first exposure to biology and Judah was very visionary, so it was a great experience for me."

Langer began to use his engineering skills to develop polymer delivery systems for the controlled release of large-molecule cancer drugs, and published a landmark paper in Nature proving that you could deliver molecules of any size or charge using polymers, an approach that had previously been thought impossible. He regards this work, and his collaboration with Jay Vacanti on using polymer scaffolds to create new tissue, among the biggest highlights of his career so far. But making this happen involved some tough decisions. "It was difficult to turn away from an obvious career and then to stick it out at MIT when it looked like I might not get tenure or be promoted. Many years later it's easy to look back on it and see it as a good decision, but at the time it was very depressing."

> "There may be many times when you try to do something in science or engineering that people tell you is impossible. But I like to think if you believe in yourself, if you really stick to things, there is very little that is really impossible."
>
> ROBERT LANGER, 1998, WHEN AWARDED THE LEMELSON–MIT AWARD

Langer modestly believes there was a certain amount of serendipity involved in his career progression and says that he was lucky to be in the right place at the right time. "Certain decisions I made were fortuitous. For example, how could I ever have known that biotechnology would emerge to be so important? But I think it's always worthwhile taking chances and that's the advice I would always give to my students."

Langer's students are success stories themselves, with more than 100 taking on professorships at universities worldwide and almost 200 in top positions in industry. Having the opportunity to encourage and mentor students and postdoctoral researchers to help them develop their careers is something that Langer finds rewarding, and he is very proud of their achievements. It is also part of the reason why he has never been tempted to swap academia for industry, particularly because balancing this supervisory role and his research is less of a challenge in the academic environment. "There are managerial responsibilities, but as an academic you are really your own boss. If I decide I want to follow a particular project, I can just do it. I have a great deal of interaction with industry and I enjoy that, but I also like the fact that my role enables me to work with students."

When asked what career advice he gives to his students, Langer replies: "I always encourage them to go for the top jobs. People can be insecure - I was, too, as a young scientist - and so mostly I just try to get people to believe in themselves. But also, do what makes you happy rather than rich. My parents put a high premium on being happy with what you're doing and I think it was good advice."

As for future plans, Langer is happy to continue doing what he does now. "I love coming up with new ideas and I love working with the students. I also want to get more and more of our discoveries into the clinic where they can help people."