NEWS & ANALYSIS

NEWS

Drug discovery and development highlights from 2003

NEWS IN BRIEF

PATENT WATCH

Balancing competition and patent law | Inherent anticipation of metabolites | **Double-patenting challenge**

ON THE COUCH

Lysosomal storage diseases market

Though overlooked by most major pharmaceutical companies for years, interest in lysosomal storage diseases has increased significantly.

FROM THE PIPELINE

Oxaliplatin

This platinum-based anticancer drug was finally approved in the United States, enhancing its potential for blockbuster status.

News review of 2003

A month-by-month rundown and follow-up of this year's news highlights in drug discovery

Simon Frantz

January

A second child of the nine who responded positively in a gene therapy trial for severe combined immunodeficiency (SCID) developed leukaemia after roughly 30 months, leading to a temporary moratorium on all gene therapy trials involving the introduction of retroviral vectors into haematopoietic cells. The US FDA advisory committee later recommended that each trial should be re-evaluated on a case-by-case basis. Suspicions that the retroviral vector, and not the modified gene, was responsible for the effect were confirmed by a study showing that in both cases the vector had integrated near a promoter for *LMO2*, which encodes a transcription factor required for haematopoiesis, and led to the uncontrolled clonal proliferation of mature T cells. Such non-random insertion suggests either a 'physical hotspot' of integration at the *LMO2* locus or, more likely say the study authors, that random *LMO2* insertion confers a selective advantage on cell proliferation.

February

The approval of rosuvastatin (Crestor; AstraZeneca) in Canada began a topsy-turvy year for the drug. Billed as the most potent statin available, it received approval in more than 30 countries, including the United States, for hypercholesterolaemia. By the end of November, rosuvastatin had 3.45% of the US new prescription

market for statins, which the company said was in line with its expectations. However, Germany, Spain and Norway withdrew from the approval process owing to safety concerns, in a situation similar to the cases of rhabdomyolysis observed with cerivastatin (Baycol; Bayer) before its market withdrawal. In addition, an editorial in *The Lancet* in November criticized AstraZeneca's campaign to promote rosuvastatin, noting that the marketing data are based on trials for which there are surrogate endpoints, but no clinical endpoints, whereas the use of the current most popular statins — simvastatin (Zocor; Merck) and atorvastatin (Lipitor; Pfizer) — is supported by large trials with clinical endpoints. AstraZeneca's CEO, Sir Tom McKillop, responded that such data have never been available for other cholesterol-lowering medicines at launch, and that the company submitted for approval the largest clinical database for any statin.

March

A mysterious pneumonia-like illness, transmitted by a doctor from the Guangdong region of China staying in a Hong Kong hotel, spread to become a 114-day epidemic of what became known as severe acute respiratory syndrome (SARS). SARS affected a reported 8,098 people, with 774 patients killed, and spread to many countries, including Singapore, Canada and the United States, making it the first epidemic to be transmitted by air travel. The World Health Organization's declaration on

Face masks became commonplace as millions tried to continue their daily lives in the shadow of SARS.

NG HAN GUAN/ASSOCIATED PRESS

15 March that the outbreak was a worldwide health threat triggered an unprecedented international effort to identify the causative agent and highlighted the technological advances that have been made in many research techniques. Compared with the two-and-a-half years it took to identify HIV as the causative agent of AIDS, within a month a coronavirus was identified as the infectious agent of SARS and genome sequences of the virus were obtained less than one month later. In May, the SARS-coronavirus main protease structure was obtained for the design of anti-SARS drugs, and in December a vaccine was successfully tested in rhesus macaques. The transmission of SARS has been stopped because of aggressive quarantine measures and possibly by rising summer temperatures, but as yet there is no definitive information on the animal source of the virus and when, or if, SARS will re-emerge in humans.

► April

Pfizer completed its US \$60-million acquisition of Pharmacia, which cemented Pfizer's position as the world's largest pharmaceutical company. The immediate fallout from this acquisition was that the chief executive of Pharmacia, Fred Hassan, left to become the chief executive of Schering-Plough, a company that has faced plummeting sales and legal investigations into its disclosure and pricing practices. Hassan, who brought with him his experience of turning American Home Products and Pharmacia around, immediately outlined his plan. This involved settling legal investigations with the US Securities and Exchange Commission, the creation of a team of executives and a global and integrated manufacturing supply chain, and a cut in payroll expenses by 10%.

May

After the disappointing number of new molecular entities approved in 2002, 2003 saw an upward trend in both numbers and innovation. This was highlighted by the approval of two widely anticipated first-in-class drugs; enfuvirtide (Fuzeon; Roche/Trimeris) for HIV and bortezomib (Velcade; Millennium) for multiple myeloma. Enfuvirtide, approved in the US in March and in Europe in May, is a linear 36-amino-acid peptide that blocks the entry of HIV-1 into cells by inhibiting viral and cell membrane fusion. Bortezomib is a reversible inhibitor of the proteasome, the key component in the degradation of unwanted or misfolded proteins that are thought to be overproduced in cancers. Bortezomib was approved on the basis of Phase II data just eight years after it was discovered — a sign that regulatory authorities are willing to push through compounds for which there is a large unmet clinical need.

June

Roche launched the AmpliChip CYP450, "the world's first pharmacogenomic microarray for clinical applications," to detect polymorphisms in genes encoding CYP2D6 and CYP2C19, which govern the metabolism of around 45% of prescription drugs. But in a decision that will affect all manufacturers of such gene chips, the FDA informed Roche on 29 October that the chip requires FDA marketing clearance or approval. The problem is that Roche had marketed the product as an analyte-specific reagent; that is, limited to the detection of a single analyte or a set of reagents for laboratories to use in creating their own diagnostic tests, which do not require premarket applications. But the FDA believes that the AmpliChip is an assembled device that is part of a specific test system, and will require a clinical demonstration of safety and effectiveness, which could take three years to complete.

NEWS IN BRIEF

HIV initiatives announced

The World Health Organization and UNAIDS marked World AIDS Day on 1 December by announcing a new initiative to provide more antiretroviral treatments to developing countries. Six million people worldwide are in immediate need of treatment for AIDS, and the '3 by 5' project aims to provide antiretroviral treatment to three million of these people by the end of 2005. The project will focus its efforts on sub-Saharan Africa, where treatment is scarce and more than 26 million are infected with HIV. It aims to provide support teams to get the drugs to where they are needed, and hopes to train 100,000 doctors, nurses and locals to administer antiretrovirals. The WHO will simplify and standardize treatment guidelines, help governments to choose and source drugs, and aid industry in gauging demand. Companies also announced initiatives; for example, Bristol-Myers Squibb said it would replicate its prevention centre in Botswana with another in an unspecified African country, and Pfizer will work on community outreach in Kenya.

Avastin disappoints...or does it?

A Phase II study of the much-anticipated anti-angiogenic vascular endothelial growth factor inhibitor bevacizumab (Avastin; Genentech) failed to achieve a statistically significant primary endpoint. In 209 previously untreated patients with metastatic colorectal cancer, bevacizumab plus 5-fluorouracil (5-FU)/leucovorin chemotherapy showed a 29% improvement in median survival. Although this was not significant, the magnitude of effect was not too dissimilar to the successful Phase III trial in 900 metastatic colorectal cancer patients on bevacizumab/5-FU/leucovorin/irinotecan, which led to filing for approval of the drug. In addition, the study also showed a 67% prolongation in median progression-free survival, which was highly statistically significant, in patients treated with bevacizumab/5-FU/leucovorin, compared with 5-FU/leucovorin alone. Despite the Phase II findings, Genentech said bevacizumab had been granted Priority Review designation by the FDA.

Older schizophrenia treatment as good as new

An older class of treatment for schizophrenia is as effective as a newer, costlier atypical schizophrenia treatment, according to a study published in the *Journal of the American Medical Association*. Olanzapine (Zyprexa; Eli Lilly) is thought to have fewer adverse effects, such as movement problems, than the older treatment haloperidol, which costs more than 100-times less a day per patient. But in a one-year study of 300 patients, funded by Lilly, there were no significant differences between the groups in reduction of schizophrenia symptoms or quality of life. Olanzapine did improve memory and mental functioning more than haloperidol, but was also associated with more frequent reports of weight gain. One possibility for the surprising results is that haloperidol was administered in combination with prophylactic benzotropine, which is given to improve movement side effects.

Rosenheck, R. *et al.* *JAMA* **290**, 2693–2702 (2003)

'Drugs don't work' admission triggers news response

A newspaper report in which Allen Roses, Senior VP, Genetics Research at GlaxoSmithKline, admitted that most prescription drugs do not work for most people, triggered an incredible response worldwide. Many print and online news sources picked up on an article in the UK newspaper, the *Independent*, which quoted Roses as saying, "[t]he vast majority of drugs — more than 90 per cent — only work in 30 or 50 per cent of the people." The article said "It is an open secret within the drugs industry that most of its products are ineffective in most patients but this is the first time that such a senior drugs boss has gone public." GSK explained that Roses was merely describing the importance of pharmacogenetics and simply stated a fact well known in medical research. GSK said, "[i]t is extremely disappointing that the *Independent* has chosen to misrepresent GSK, the pharmaceutical industry and the whole science of pharmacogenetics in this way." The response of other news sources implies that a large gap exists between the industry and the public's understanding of this topic.

Virtual screening competition announced

The *Journal of Biomedical Screening* and the High-Throughput Screening department at McMaster University, Hamilton, Ontario, Canada, have announced a competition to assess the validity of virtual screening and other computational approaches in identifying compounds for follow-on screening. Applicants will be given a high-quality experimental 'training data set' of 50,000 compounds against the dihydrofolate binding site of *Escherichia coli* dihydrofolate reductase, and will have to predict the activity of an additional 50,000 molecule 'test library'. The data set and library will be released on 15 January 2004 and the submission deadline for entries is 15 March, after which data will be reviewed for successful predictions.

<http://hts.mcmaster.ca/>

July

RNA interference (RNAi) seemed to be coming of age. The recently discovered process, in which genes can be silenced by small RNAs, took the biology world by storm due to its novelty, elegance and efficiency. Start-ups were quickly formed to create therapeutic applications of RNAi, and in July two of the biggest companies in this field, Alnylam and Ribopharma, merged. July also saw the publication of the first of two papers published in 2003 that raised questions about the specificity of RNAi. Both showed that the RNAs used to silence genes could also activate genes in the interferon-response pathway, which triggers global inhibition of endogenous messenger RNA translation and leads to apoptosis. The effect of the interferon response *in vivo* is not yet certain, and many reasons have been proposed for the observations: for example, high concentrations of RNAs might affect what is a natural, saturable system. Nevertheless, in September, Merck and Alnylam entered the first major collaboration between a pharmaceutical and an RNAi company to develop therapeutics.

August

With great sadness, 2003 saw the passing away of three well-recognized figures in the pharmaceutical industry. Louis Lasagna, the founder of the Tufts Center for the Study of Drug Development and widely regarded as the creator of clinical pharmacology, died on 6 August. Lasagna revolutionized drug evaluation and regulation by promoting randomized controlled clinical trials as the gold standard, and argued that it was essential to consider the placebo response in trials. On 1 April, David Horrobin died. One of the central themes of Horrobin's research was the role of fatty acids in disease, such as neurodegenerative disorders. A passionate, persuasive and often controversial man, Horrobin was the founder and editor of *Medical Hypotheses*, which allowed the dissemination of new ideas in medicine, and was a strong voice in highlighting inefficiencies in the

New agreements gave poor countries greater access to generic medicines. ERIC MILLER/WHO

pharmaceutical industry. Finally, Paul Janssen, creator of Janssen Pharmaceuticals, died on 11 November (see editorial in this issue).

September

After almost two years of discussions, the World Trade Organization finally agreed on a breakthrough deal to give poorer countries access to generic medicines. The Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement established at the Doha meeting in November 2001 gave countries facing public health crises the right to override patents on vital drugs and order generic alternatives, but only from domestic producers. In an emotional plea, African negotiators overcame last-minute hitches by stressing that 2.2 million Africans had died of AIDS and other epidemics during an eight-month deadlock in the talks. The new agreement allows poorer countries to import generic drugs when necessary, but lists a number of rich countries that will refrain from importing generics and less-rich countries that will import them only in circumstances of extreme urgency. Almost instantly, Brazil authorized the importation of generic antiretrovirals, and the Canadian government announced in late September that it would amend patent laws to allow manufacture of generic medicines.

October

The 2003 Nobel Prize in Physiology or Medicine was awarded to Paul Lauterbur, of the University of Illinois, Urbana-Champaign, and Peter Mansfield, of the University of Nottingham, UK, for their contribution to the development of magnetic resonance imaging (MRI) as a medical tool. Lauterbur adapted nuclear magnetic

resonance (NMR) by introducing gradients in the magnetic field, and Mansfield developed the use of gradients in the magnetic field and showed how the signals could be analysed, which made it possible to develop the technique into a useful clinical imaging tool. Raymond Damadian's protest that he deserved a share of the prize because he showed that cancerous and healthy tissue can be distinguished by their different NMR signals was unsuccessful, despite spending thousands of dollars on full-page advertisements in US newspapers asking readers to protest by contacting the Nobel committee.

November

The US Senate finally passed the Pediatric Research Equity Act, which gives the US FDA the authority to require pharmaceutical companies to test treatments for use in children. Around three-quarters of drugs on the market have not been tested in children and are used off-label, with clinicians obtaining dosing regimens from extrapolation of data from adults to children. Companies were not required to test medications in children until the FDA adopted the Pediatric Rule in 1998. But in October 2002, a federal court overturned the rule on the grounds that companies could not be required to study indications that they did not want to study. The FDA said that this in effect reduced children to an indication rather than a disenfranchised group and the same could be applied to, for example, ethnic minorities or pregnant women. Instead of appealing, the FDA successfully relied on Congress to codify the rule into law.

December

A contrast in short-term fortunes of the second and third biggest pharmaceutical companies was revealed this month. GlaxoSmithKline held its first R&D day since the merger in December 2000, and said its pipeline had grown to 147 projects in clinical development — including 82 new chemical entities, 45 product line extensions and 20 vaccines — with 20 of these compounds having the potential to become blockbusters. However, news of the pipeline resulted in shares dipping slightly by 1%, as investors were disappointed by the lack of late-stage compounds. Merck, which has refused to pursue the consolidation route, found itself in the unusual situation of terminating two Phase III compounds in the space of two weeks — aprepitant, a substance P antagonist for depression, and MK-767, a peroxisome proliferator-activated receptor (PPAR)- α and PPAR- γ agonist for diabetes. To strengthen its pipeline, Merck has recently formed alliances with Actelion to develop renin inhibitors for hypertension and with Neurogen to develop small molecules that target the vanilloid receptor for pain.

The approval of enfuvirtide (top) and bortezomib (bottom) highlighted a more promising year for approvals.