Hope and hype for cancer drugs

The year 2003 saw no shortage of cancer headlines—from the approval of several new cancer drugs to the increasing application of genomic and proteomic technologies to classify and predict cancer. But recent successes have not been unequivocal, and emphasize the need for tempered optimism.

The antiangiogenesis drug Avastin, in combination with other therapies, showed promise in extending survival of patients with advanced colorectal cancer, but a second, smaller trial did not corroborate the results. The US Food and Drug Administration (FDA) approved Velcade—a proteasome inhibitor—for multiple myeloma, and the tyrosine-kinase inhibitor Iressa for advanced non-small cell lung cancer, but neither drug’s clinical potential has yet been adequately confirmed. Still, the Swiss equivalent of the FDA has approved Eribitux, a monoclonal antibody to the epidermal growth factor receptor—one of the tyrosine kinases targeted by Iressa—for drug-resistant colorectal cancer. Antisense approaches such as Genasense, which is directed against the tumor cell survival gene BCL2, continue to disappoint. Despite these setbacks, the FDA has pledged to accelerate approval of cancer drugs and, along with the US National Cancer Institute, to double the number of phase 3 clinical trials for those drugs.

Infectious diseases: beyond the usual suspects

2003 kicked off a new threat to public health—severe acute respiratory syndrome (SARS). Emerging from Guangdong, China, in November 2002, the mystery virus quickly became a global threat by April 2003 (Nat. Med. 9, 487; 2003). At record rates, researchers identified the culprit—a new coronavirus—and its receptor, angiotensin-converting enzyme-2. The virus may strike again, so the hunt is on for effective treatments (Nat. Med. 9, 806; 2003) and for a vaccine (see News, page 9).

SARS created an epidemic of nervousness, but the death toll was modest: it killed fewer than 800 people. What did 2003 mean for the bigger killers? Few seemed surprised by the failure of VaxGen’s HIV vaccine (Nat. Med. 9, 376; 2003). On the brighter side, the US Food and Drug Administration approved a new class of HIV drug—a fusion inhibitor called enfuvirtide. Two phase 3 clinical trials showed that enfuvirtide, in combination with other antiretrovirals, can suppress HIV replication in people who no longer respond to available therapy.

The year also saw nations around the world begin publicly addressing their HIV crises. In August, the South African government agreed to provide antiretrovirals to its citizens. More recently, India and China have followed suit. Good news also came for other infectious diseases: the Bill and Melinda Gates Foundation donated $168 million to fuel a renewed effort to fight malaria, which affects more than 300 million in the developing world.

Stem cell fusion raises specter of confusion

Stem cell research took a new turn in April 2003, when two independent studies suggested that bone marrow cells are not as versatile as previously believed. Rather than differentiating into liver cells, transplanted bone marrow cells instead fuse with host liver cells, groups led by Markus Grompe and David Russell reported (Nature 422, 897–901; 2003 and Nature 422, 901–904; 2003). The news followed reports from 2002 of fusion events in cell culture.

The new shifts the emphasis in therapeutic applications away from inducing differentiation, which posed a daunting challenge given the number of target cell types. Promoting cell fusion—by harnessing viral genes that promote fusion, for instance—has instead risen to the top of the agenda. Although the shift in emphasis might simplify stem cell therapies, the mangled karyotypes resulting from fusion raise the specter of cancer. Predicts Grompe, “I think that what we are going to see in 2004 is that fusion can be an important tumor progression event.”

Hormone replacement takes another hit

The debate on hormone replacement therapy (HRT) for postmenopausal women precipitated in the summer of 2003 when results from long-term trials indicated that, contrary to prevailing hypotheses, combination hormone replacement doubles the risk of dementia, including Alzheimer disease.

The Women’s Health Initiative (WHI) was launched in 1998 to evaluate the effects of different HRT treatments. One arm of the trial—testing a combination of estrogen and progestin, the most commonly used form of HRT—was abruptly cut short in 2002 when preliminary results indicated an increased risk of breast cancer.

Various reports published throughout 2003 also indicated higher risks of heart disease, stroke and ovarian cancer, which may outweigh the known benefits of this form of HRT. What is not yet clear is how these results extrapolate to other forms of HRT. It will be crucial to compare the current data with results from the ongoing estrogen-only arm of the WHI to weed out the potential effects of progestin.

‘Bubble boy’ trial delivers blow to gene therapy

The gene therapy field suffered a setback in 2003 when researchers unraveled the mechanism underlying serious complications in a clinical trial once hailed as a landmark success. Alain Fischer’s group at the Necker Hospital for Sick Children in Paris used a retroviral vector to treat X-linked severe combined immunodeficiency—the so-called ‘bubble boy’ disease. But after 2.5 years of success with the therapy, two of ten patients developed a T-cell leukemia–like disease, later shown to be a result of the retrovirus inserting itself near the \textit{LMO2} proto-oncogene (Science 302, 415–419; 2003).

Although scientists had long been concerned about the risk of insertional mutations, studies in animal models had not supported their fears. Results from the French trial dealt another blow to an already-chastened field (Nat. Med. 9, 977; 2003). Regulatory agencies in the US and UK have since allowed related trials to proceed with extra caution, and researchers are designing safer vectors and protocols for future trials.