

Week 2: Medical Issues Extended Reading**Up close and Personal**

Source: *The Economist*, October 16th, 2004, pp 71-74.

Try not to use your dictionary when you read the text below. Instead, look at new words and try to decide whether you need to understand the text in order to understand the main points in the text. If you really need the word, then try to work out its function in the sentence. Once you have done that, look for clues in the sentence itself and in the surrounding text. Try to work out the approximate meaning for yourself. The questions will help you to pick out the important points that you should focus on.

Pre Reading

1. Skim the text by reading the first sentence of each paragraph quickly. What is the main idea of the text?

2. Scan the text and find out why the following dates are important.

Date	Why is this date important?
1970s	
1971	
1990	
2000	
2001	
2010	
2010 or 2011	

Reading Guidelines

The reading guidelines are designed to give you practice in identifying key ideas. Remember, you don't need to read everything in order to understand the main points in the text. This will give you practice for both tests and your future academic reading requirements.

1. Read lines 1-20

a) Why has there been an increase in cancer rates?

b) Why are scientists optimistic?

2. Read the section called Multiplication and division.

a) According to the text, what is cancer?

b) What do the current therapies do?

- c) What drugs are mentioned in the text?
- d) What do researchers need to do now? Why?

e) Why do you think this section is called Multiplication and division?

3. Read the section called The need for combinations.

a) What do the academic community and pharmaceutical companies agree on?

b) What do the academic community and pharmaceutical companies disagree on?

c) Why do you think this section is called The need for combinations?

d) What combination therapies are mentioned?

4. Read the section called Picking the right target.

a) What is most promising at the moment?

b) What kind of personalised care is available at the moment?

c) What will TRANSBIG do?

d) Why is this section called Picking the right target?

5. Read the section called Look to the future now.

- a) What is appearing on the market at the moment?
- b) What other approaches are being considered?

c) What other ideas are circulating at the moment?

d) Why is this section called Look to the future now?

GOING by the numbers, humanity seems to be losing the war on cancer. According to the most recent data from the World Health Organisation, 10m people around the planet were diagnosed with the disease in 2000, and 6m died from it. And these numbers are growing. With an ageing population, the spread of western-style diets, and increasing tobacco consumption, cancer is on the rise around the globe. In America, for example, projections suggest that 40% of those alive today will be diagnosed with some form of cancer at some point in their lives. By 2010, that number will have climbed to 50%. All this is despite the fact that, since then president Richard Nixon's famous speech in 1971, launching what became known as the war on cancer, America has given nearly \$70 billion (in actual, not inflation-adjusted, dollars) to its National Cancer Institute (NCI). And that is not to mention the money spent by drug companies and charities – nor, indeed, the re- search budgets of other countries. Despite these billions, the rate of death from cancer in the United States has increased from 163 per 100,000 individuals in 1971 to 194 per 100,000 in 2001. By contrast, mortality rates from heart disease and strokes, two other diseases often seen as being associated with affluent styles of living, have fallen (see chart 2 overleaf).

Luckily, these numbers do not tell the whole story. In fact, scientists are optimistic about the future of cancer treatment – very optimistic. As Paul Workman, director of the Cancer Research UK Centre for Cancer Therapeutics, a charity, puts it, "This is the second golden era of cancer research." While no one expects a cure for cancer in the next decade, many think it could be demoted to the status of a chronic disease that people can live with – in other words, something more like diabetes.

Multiplication and division

Cancer is characterised by uncontrolled cell growth. Healthy cells regulate their division into daughter cells carefully, subordinating their own Darwinian tendency to reproduce in favour of the survival of the body they inhabit. It is one of the marvels of evolution that they are able to do this, and so allow the development of multicellular creatures. But evolution works on many levels, and it is almost inevitable that mutations in some of the trillions of cells that make up a human body will disable the regulatory genes. Then it is just a matter of the survival of the fittest among cells. In a competition between regulated and unregulated cells, the unregulated ones will multiply faster, and win. The result is cancer.

35 Most current therapies – drugs that were developed during the first golden era in the 1970S – simply attack dividing cells. That stops tumours, but it also kills all rapidly proliferating cells, regardless of their origin, function or state of health. The action of these drugs on normal tissues causes the side effects, including nausea, fatigue and weakened immune systems, associated with cancer treatment. By contrast, the new generation of drugs, several of which are already in the clinic, attack only deranged cells. These drugs are designed to fix the specific molecular problems in a tumour that drive its growth. The best known of these new drugs is Gleevec (or Glivec, depending which side of the Atlantic you live on). It was designed to halt a blood cancer called chronic myeloid leukaemia (CML), 40 which is characterised by the over-proliferation of white, myeloid blood cells. CML is caused by the union of two chromosomes, numbers 9 and 22. When these chromosomes break, and their parts then join to form a 9-22 hybrid chromosome, they bring together two genes, called BCR and ABL. The novel protein made by the gene which results from this union is known as BCR-ABL. (A medical convention distinguishes the names of genes from the names of the proteins they produce by italicising the former.) BCR-ABL is one of a class of enzymes known as tyrosine kinases, which are 45 involved in signalling pathways within cells. In the case of BCR-ABL, the signal generated tells the myeloid cells to proliferate continuously. Gleevec blocks the activity of BCR-ABL by sitting in the enzyme's active site. This switches off the signal to grow, and the cancer stops proliferating.

50 While the details of the molecular damage behind CML may seem arcane, they are central to the success of Gleevec and drugs like it. Without such information, the likelihood of stopping a disease with targeted drugs is small.

55 The story of another targeted molecule, Iressa, illustrates that point. Iressa blocks the activity of a different tyrosine kinase, called EGFR. This enzyme is present in many types of healthy cell, but is over-abundant in 80% of lung cancers. Given this pattern, and the fact that EGFR, like BCR-ABL, stimulates cell division, researchers hypothesised that the drug would be an effective treatment for the majority of lung-cancer patients. Instead, only about 10% of such patients had a strong response to Iressa – although the disease's progression was slowed down in another 30-40%. 60

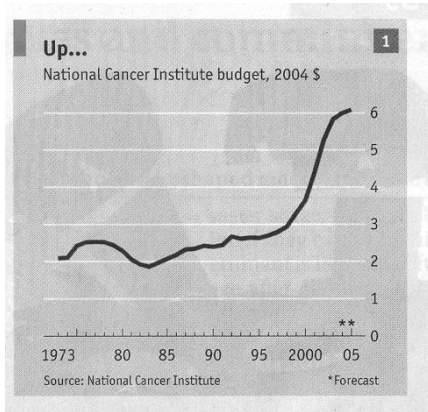
65 Three studies published over the summer explain this lower-than-expected response rate. The patients who responded strongly to Iressa not only had lots of EGFR, they also had a mutant form of the enzyme. By contrast, those patients who had either no response or a partial response may have had an over-abundance of EGFR in their tumours, but it was the normal version of the enzyme.

70 That finding points to a crucial requirement for the new drugs that was not necessary with the old sort: careful patient selection. To deploy targeted therapies effectively, researchers need to find ways to identify those patients who will respond and those who will not. Otherwise, not only will drugs that have been approved for use be wasted on those who cannot benefit, but useful drugs may look useless when they are being tested for regulatory approval-and may thus be rejected altogether.

75 The elucidation of why some patients respond to Iressa and others do not proves that targeted therapies will work, according to Brian Druker, from Oregon Health Science University in Portland, who developed Gleevec. As long as researchers understand the crucial molecular abnormality in a cancer, design a drug to fix that problem, and use it in only in patients who have that molecular anomaly, then such targeted therapies can be effective.

The need for combinations

80 In general, the academic community and pharmaceutical companies agree with this assessment. Where they differ is on the likelihood of identifying one key mutation that underlies a given cancer.



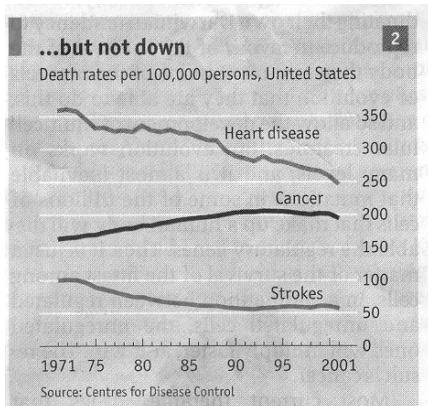
85 CML is unusual because only one mutation, the chromosomal junction between the *BCR* and *ABL* genes, drives the disease. By the time most cancers are diagnosed they have four or five mutations that researchers think contribute to the disease. That means one "silver bullet" drug is not likely to act as a cure, and may not even slow things down much.

90 Given the complexity of the problem, then, researchers see a need to combine several drugs into a therapy so that several mutations can be treated simultaneously. That is not, it must be said, a new idea. Combination therapies are standard for most cancers.(and also for AIDS). But most existing treatments include several of the traditional, non-specific drugs. The trick now is to work out how to build successful combinations using the new generation of targeted drugs.

95

The first such combinations, which are already in use, merge alone targeted therapy with one or more traditional agents. For example, Herceptin, an antibody-based drug that stops the activation of a cell-surface receptor protein called HER-2, is often paired with traditional therapies in breast-cancer care. In such regimens, the targeted therapy's role is to make the tumour particularly vulnerable to the traditional drugs. The problem with such combinations is that they do not make the traditional drugs any less toxic. So, while they may improve a patient's prognosis, they are not a panacea.

100



105 A more forward-looking approach is to try to combine several targeted agents. In one example, researchers at the Sarah Canon Cancer Centre in Nashville, Tennessee, have tested the combined ability of two drugs to treat kidney cancer. Avastin blocks angiogenesis (the formation of the new blood-vessels which feed and oxygenate a growing tumour) and Tarceva is another inhibitor of EGFR. When presented at a scientific meeting in June, the work was lauded as the beginning of a new trend.

110 However, it is not yet clear whether his particular combination is really any letter than tyrosine kinase inhibitors are when they are used alone.

115 Science aside, the next big hurdle for combination therapy is the issue of intellectual property rights, according to Richard Pazdur, director of Oncology Drug Products at the Food and Drug Administration (FDA), the organisation that regulates medicines in America. Companies will have to find ways to combine and test their drugs with those of others, in order to produce the best combinations possible.

120 Although several company executives have expressed a disinclination to test their drugs in combination therapies before approval, Dr Pazdur is emphatic that the agency will consider – and encourages – such trials, as long as there are scientific data to support the approach. Furthermore, many researchers see these efforts as necessary for the success both of individual drugs and of progress in the field as a whole. Some drugs may not have sufficient power to be approved on their own, but would do so if evaluated in culmination with others, according to Daniel Ton Hoff, an oncologist at the University Of Arizona, in Tucson. Thus developers who hesitate to put their new product into such tests may lose out in the end.

130 **Picking the right target**

All this targeted therapy, though, will be of little use if it is aimed at the wrong target. And that points to the other part of the second golden age of cancer treatment, which is not treatment at all, but better diagnosis.

135 The most promising new diagnostic echnology is the DNA microarray (or “gene chip”, as it is colloquially known). Gene chips can do two things that are relevant to cancer diagnosis. They can identify mutations in particular genes, and they can monitor the activity of lots of genes at the same time-showing a doctor which genes in a tumour are busier than they should be, and which are less busy. Such chips have been crucial in dividing what appear, under the microscope, to be single diseases into smaller groups based on their precise molecular biology (as in the case of lung cancer mentioned earlier). And it is gene-chip technology that is most likely to usher in the era of “personalised medicine”, which many see as the future of medical treatment, and in which a “read out” of a disease's details will result in an individually tailored treatment.

145 To a limited extent, such personalised care is already available. Breast cancers, for example, are regularly tested for the over-expression of HER-2, and only those patients whose cancers have the protein are treated with Herceptin. But the TRANSBIG clinical trials group, based in Brussels, intends to go further. It started a trial earlier this year to determine whether microarray data can be used to identify which breast cancer patients need back-up chemotherapy after surgery, and which can get away without it.

150 At the moment, the vast majority of breast-cancer patients receive such post-surgical treatment (95% in the us and 85% in the EU), even when their lymph nodes appear disease-free, and thus they would seem to be at limited risk of cancer cells spreading to other parts of their bodies. It is clear that only a few of these women gain a significant benefit from this additional therapy, while most suffer its side effects. Unfortunately, researchers have been at a loss to distinguish between those who can safely skip chemotherapy, and those who cannot. The TRANSBIG trial will assess the ability of microarray data to distinguish between these two groups by testing 5,000 women for the expression patterns of 70 genes. This is the first trial to test the ability of microarray data to direct clinical decisions. It will be completed in 2010 or 2011.

Look to the future now

165 The targeted drugs now appearing on the market should, if all goes well, be just the first wave of new anti-cancer therapies. The armoury will expand rapidly over the next five years as more targets are identified, and new classes of drug pass muster with the regulators.

170 For example, one target that researchers think promising is a gene called B-RAF. The protein from this gene is overexpressed in 80% of melanomas (a type of skin cancer) and in 20% of cancers of the colon and rectum. Besides being a likely target, it is thus also an example of something that might cause oncologists to shift the way they look at their subject, and start classifying tumors not on the basis of which tissue is affected, but which gene, or genes, have gone wrong.

175 As to the drugs themselves, one class that is likely to grow over the next five years is that based, like Herceptin, on antibodies. An antibody is a protein produced by the immune system to knock out an infectious agent such as a bacterium. Each antibody molecule has two sites specifically tailored to lock on to a protein that occurs in the invader but not in the human body. However, antibodies that stick to human proteins can easily be made in the laboratory. And if the protein in question is found mainly in tumours, the antibody might – as in the case of Herceptin – make a good drug.

180 Even if it does not, however, it can be used as a delivery van for a drug that does work, but which is too poisonous to be allowed to wander freely through the body. Nor does the payload have to be a drug. It can be a radioactive isotope – allowing radiotherapy designed to kill tumour cells to be directed to those cells alone. Several such drugs have already proved their value in blood cancers, 185 substantially improving the treatment of diseases such as non-Hodgkin's lymphoma. Antibodies also form the basis of Avastin. And such anti-angiogenesis drugs are a further promising avenue of research.

190 Another approach is to try to recruit the immune system directly, by stimulating it with a vaccine and possibly bolstering it with extra antibodies to attack the tumour as though it were an invader. Such immunotherapy looked promising in the past, but ultimately failed the challenge.

195 At that time, the thought was that a response sufficient to destroy a full-blown tumour might be stimulated. This, researchers now understand, was too much to ask, according to Jedd Wolchok at the Memorial Sloan-Kettering Cancer Centre, in New York. Instead, these therapies might serve to limit the recurrence of tumours, or to kill stray cancer cells left over after the bulk of a tumour has been removed by the surgeon's knife. Researchers are therefore eagerly awaiting the first results from a big clinical trial of a vaccine called Canvaxin. If this trial, which is directed against malignant melanoma, works, it will provide an important proof of concept for other immunotherapies.

200 And there are even wilder ideas around. In the early 1990S, researchers in California conceived of modifying an adenovirus (the sort that causes colds) so that it would kill cancer cells, and those alone. The first tests were unsuccessful, but since then investigators have tweaked the virus and think they have aversion that is likely to work. They hope to start the first phase of clinical tests with the new virus in brain-cancer patients later this year. Meanwhile, another group is testing a similarly modified virus in patients at high risk of developing mouth cancer. In this case, the virus – which is intended to stop a tumour developing in the first place – is delivered as a mouthwash. The most important change of all, however, will be early diagnosis, according to Lee Hartwell, the director of the Fred Hutchinson Cancer Research Centre, in Seattle. The more advanced a cancer is when it is diagnosed, the more 205 likely it is that the tumour will already have developed genetic tricks to escape even the best drugs. Even a pea-sized tumour has a billion cells. That provides it with a lot of chances to evade treatment. Already, body scanning, in the forms of computerised tomography, magnetic-resonance imaging and positron-emission tomography, provides physical and chemical detail far beyond that available during 210

215 the first golden era of cancer research. Within the next decade, these techniques will be combined
with new radioactive and fluorescent probes that will enable doctors to see small clumps of precancer-
ous cells. Edison Liu, executive director of the Genome Institute of Singapore, likens this to a
"Starltekian" scan of the body, in which doctors may be able to see clumps of deregulated growth
containing as few as ten cells. They will also be able to tell what molecules are causing the problem.
220 So if, for example, a patient's EGFR is out of whack, they can treat him with a molecular inhibitor such
as Iressa or Tarceva well before any symptoms appear. With tools like this available, it may be that
having a 50% probability of being diagnosed with cancer if you are an American will prove to be an
underestimate. But your chance of actually dying of the disease will soon, itself, be dying.