

How new technologies in computing, molecular biology, physics and robotics are reasons to believe our children will not fear cancer.

In the late 1960's, Richard Nixon declared his "war on cancer". The USA was flush from its successful Apollo moonshot program that John F. Kennedy had launched almost 10 years before. Like the space program, the war on cancer campaign was ambitious, far-sighted and technically demanding. What Nixon (and his advisors) did not realize was that putting a man on the moon was a cake-walk compared to curing cancer. That isn't to say that there hasn't been significant progress in treating this collection of diseases - it has just proven a much tougher adversary than gravity and distance.

The space race succeeded because scientists and engineers pushed back frontiers of knowledge. New materials were invented, new manufacturing techniques devised and there was a plan. Cancer scientists use equally complex tools and weapons against this disease. Precision-guided X-ray machines use robotics and remote controls that allow exquisite definition of the tumour. Imaging techniques such as computer assisted tomography and magnetic resonance imaging allow physicians to literally see the malignant cells from outside of the patient. Micro-pumps can be implanted to deliver metered doses of chemotherapeutic agents. There's even a camera that's the size of a large pill. After being swallowed, it transmits pictures of the intestinal lining as it traverses the digestive system, generating a virtual movie and identifying diseased tissues. Fortunately, its one-use only.....Over the past 40 years, progress in cancer treatment has been largely incremental. As a part of the war on cancer, the National Cancer Institute (NCI) in America, as well as laboratories around the world, began to systematically screen for drugs that slowed or stopped the growth of cancer cells. This yielded a bumper crop of agents that were little more than poisons and mutagens. Most of these agents target rapidly dividing cells by introducing lots of errors into DNA or causing the DNA production machinery to become clogged. The dividing cell population includes most (but not all) cancer cells but also various normal cells which have short lifespans - such as the cells that line the intestine and blood cells. The dose at which the drugs are effective in killing the cancer cells is usually high enough to kill some of these normal cells causing dose-limiting side-effects. As a consequence, a fine line has to be drawn between trying to kill as many tumour cells as possible while sparing the good guys.

Before a cell can divide, it must duplicate its DNA. Normally, this is a very precise process and if a mistake is made (where just one out of over 3 billion parts of the DNA that constitutes our "genome" is incorrect), the cell detects the error and halts the cell division process until the error can be repaired. If it can't, the cell commits suicide. Since we're made of trillions of cells, losing a few here and there is a small price to pay to prevent the occurrence of a mutation. Repairs are going on all the time. Every day, thousands of mutations are introduced into the DNA in each one of our cells. It goes with living on a planet bombarded by solar rays and being bathed in oxygen. Fortunately, we have extraordinarily efficient micro-machines that constantly repair this damage and keep our DNA on the straight and narrow. That isn't the case in cancer cells where the repair machinery is often defective. This allows cells to accumulate mutations. Most of these actually kill the tumour cells but there are so many of them that there are always a few that get through. As the maxim states, "what doesn't kill me makes me stonger". Over time, the tumour cells evolve via natural selection to become insensitive to the checkpoints that usually monitor cell growth and they take off.

So, we have genetically unstable cells that are about to be treated with chemotherapeutic agents that act by introducing more mutations (X-irradiation does pretty much the same thing!). If there are not enough mutations introduced by the chemotherapeutic agent to kill the cell, it might actually result in the evolution of some new tumour property. That's one of the mechanisms by which cells become resistant to drugs (and radiation). Often we hear about patients being treated and going into remission. The tumour cells recede and all appears to be well. Sometimes, however, the tumour cells grow back - causing a relapse. These cancer cells must have missed being killed by the drug - why not simply repeat the treatment? Unfortunately, the returning cells are usually quite different animals from their original tumour ancestors and have often become a little bit more resistant to the drug - enough that the dose of agent now required to kill them would also kill the patients' normal cells. Even more sinister is that these cells often show resistance to drugs that they've never encountered. This "multi-drug" resistance effect is extremely difficult to deal with - it's as if the tumour cells can mind-read the physician and dodge the on-coming bullets. In fact, what the cells have often stumbled upon is the protective effect of pumps that normally eject certain molecules from the inside of a cell to the outside. These pumps can also suck out the drugs and are quite promiscuous about the type of drug they'll eject. The obvious consequence is that the concentration of the drug inside the tumour cell is reduced which has the same effect as reducing the dose.

Many of the drugs identified in the Sixties are in use today. They are most widely used in combinations as this is more effective, but they tend to do much the same thing. They are dose-limited by their toxicity and usually have lousy side-effects. Advances continue to be made, but they tend to be refined and small. A big clinical trial involving hundreds of patients may show that a particular combination and dose regimen improves 5 year survival by 9%. This becomes standard practice. The mortality rate is slightly improved. Such advances have nibbled at the overall burden of cancer but because the population is aging, the number of new cases is always increasing.

Let's step back a minute and ask why these drugs are not very good? Why is the cure rate so low? Part of the answer lies in the dose-limitation discussed above. These drugs and radiation therapies are essentially lethal weapons and cannot simply be ramped up until the cancer has disappeared. In any case, how can we be sure of getting every tumour cell? Another part of the answer derives from how these drugs were identified and tested. Various tumour cells were grown in laboratories or grown under the skin of mice (so called "xenografts"). The cells or the mice were treated with the drug and the rate of cell or tumour growth

measured. As was noted in the previous article, it is much easier to cure cancer in mice than people. This is because we stack the decks in the mouse experiments. We introduce a stable, fast growing cell type then shoot drugs into it. We don't wait 6 months to see if all traces of the artificial tumour have gone (mice have an average lifespan of 2 years or so, so 5 year survival studies aren't possible). Of course, mice are used because it is ethically impossible to experiment on people in this way (introducing tumour cells into a healthy person) and why would anyone want to do that in any case? Actual cancers are not engineered in a laboratory. They incubate over tens of years, evolving and spreading as they make their way through the obstacle course towards a full fledged tumour. By the time they're detected, they've become a professional army and they've dug in.

Part of the problem is therefore that the wrong models are being used to test for drug efficacy. Our models are too simple and we don't understand enough about the natural enemy. This is changing as new animal models are being developed. Instead of injecting tumour cells, there are models in which certain activated, cancer promoting genes are inserted into the mouse DNA. Over time, these mice develop a more natural form of cancer that more closely resembles the human disease. This has been made possible by advances in genetic engineering that allow genes to be inserted or deleted. For example, work from around the world has identified a certain type of gene that is commonly lost in cancer cells. It's thought that these genes normally act to inhibit cancer growth (a sort of cellular policeman) and they are therefore called "tumour suppressors". The cancer cell inactivates the policing genes and is then free to run rampant. Due to the remarkable similarity between our genes and those of the mouse (which can be over 95% identical), the mouse counterpart to the human tumour suppressor can be selectively inactivated, generating a line of mice that lack that gene. These mice usually have a greater tendency to develop spontaneous cancers.

Besides better models, there are immense research efforts that are focussing on other means to kill tumour cells. I mentioned previously that normal cells commit suicide rather than allow a mistake to be immortalized into their DNA. Tumour cells still have the suicide machinery intact (in fact, this is how conventional chemotherapeutic drugs work). What if we could trick the cancer cell into pulling it's own trigger? We also have developed a good understanding of the command and control systems that regulate cell functions. By taking out a few strategic molecules, the cell's "generals", the tumour cell can be thrown into a tailspin. The best example of such smart drugs is Gleevac, a drug that inhibits a particular protein that is activated in chronic myelogenous leukaemia (CML). This is a very difficult cancer to treat as it inexorably progresses from a controllable disease into a crisis phase. Gleevac specifically blocks the function of the abnormal protein. It is therefore essentially non-toxic, it also usually cures the cancer. If only there were more drugs like this!

The problem is that in the early stages, CML is completely controlled by the target of Gleevac. 95% of the patients with CML have the altered and activated protein. It is a "homogeneous" disease. This is not the case for most other cancers. Cancers of the breast, prostate, ovary, colon, brain, etc. are heterogeneous and highly variable. Ten patients presenting with the same diagnosis usually have ten different manifestations of the disease. This is not too surprising given that each person has been incubating their particular disease under very different circumstances (different exposure to carcinogens, foods, environmental agents, etc, not to mention their genetic differences). To increase the chance of treating these patients optimally, we have to find their particular Achilles heel(s), just like in CML. New drugs are in the pipeline, but how can we determine which drug is most appropriate for which patient? There isn't time to test them all on each patient.

Enter a new technology that is like an X-ray machine for your genes. Each of our cells contains 30-40,000 genes. Almost all of these are identical between each of our cells but they differ by about 0.1% (one in a thousand) from your friends, neighbours and any other human on the planet. While each cell contains this same genetic repertoire, the relative activity of these genes is highly variable. Lets consider the 30,000 odd genes like a humongous deck of cards. Each cell has the same deck but only some of the cards are turned right side up and the cards that you can see in one cell may be different in another cell. You'd expect this, because these genes might be involved in pigment formation in the skin or acid secretion in your stomach - specialized functions of different tissues. Many of the upturned cards are the same in all cells. These are the house-keeping genes that all cells need for their day-to-day activities.

The number of upturned cards does not remain static. Cards are continuously being turned over or hidden in response to changes in the environment. Where the analogy breaks down is in the concentration of the cards. Our genes are activated to different levels in our cells, not just turned on and off, like turning a card over. Think of our DNA as a very thick book with bits of genes being dispersed throughout. When the cell wants to activate a gene, it starts a process that extracts the words corresponding to the gene from the text and pastes them together to form a coherent paragraph. There are two copies of the book in each cell (one inherited from the father, one from the mother) but the numbers of paragraph copies made can be just one, one hundred or one thousand, depending on the instructions. The words in the paragraphs are in a similar format to those in the book, but they have been edited together. This "transcription" process must undergo yet another conversion to make proteins. Here, there has to be a transformation from words from one language to another - that of amino acids which are the building blocks of proteins. This process is called "translation" and generates the proteins that carry out the bulk of the functions within a cell.

In any cell at any time, there are therefore thousands of changing events - a bit like a monster graphic equalizer display with each gene bouncing up and down or staying constant over time. One way to grab a snapshot of this complexity is to freeze-frame the cell and count the number of paragraphs associated with each gene. This would tell us which genes are on and how active they are. Until 5 years ago, we could only do this one gene at a time which is a bit like trying to steer a car while looking through a telescope. To get a better view of the gene landscape, various researchers built devices that could print each gene onto a surface the size of a postage stamp in a precisely controlled array. This micro tapestry of genes could then be used like miniscule fly paper to pull out the various paragraphs from a tissue sample. By marking each paragraph with a detectable flag, the number of copies of each flag and thus the number of copies of the paragraph can be determined. Because the position of each type of paragraph on the tapestry is known, it's a simple process to measure the relative concentration of each paragraph/gene. Up to 30,000 different genes can be printed onto these "microarrays" which allows one person to generate the same results in one day that previously would have required the efforts of all the cancer researchers in the world. Applying this technology to cancer allows researchers to determine the fingerprint or profile of any tumour. The computational analysis is complicated, but helps researchers simplify the data so that it can be more readily understood. These genetic fingerprints contain a wealth of information. For example, they may point to suspicious genes that are over active in a tumour allowing other researchers for

assess them as potential drug targets. They help improve the mouse models by providing detailed comparisons of how close the models reflect the human disease. By constructing a tumour fingerprint database which associates each complex gene activity pattern with known outcomes, treatment responses or survival rates, a reference atlas is created against which a newly fingerprinted tumour can be compared. This should allow more precise diagnosis and better optimization of treatment. The dream is to be able to treat each patient with a customized therapy that is designed specifically to eliminate their particular tumour. Such designer treatments would exploit the specific vulnerabilities of the tumour and avoid therapies to which the tumour is already resistant. The dream is not so far from reality. Already, researchers have identified new classes of cancer based solely on microarray analysis. Pairing this information to treatment responses will ensure the best medication is used against each tumour.

There's no doubt that the war on cancer is far from over but the new hi-tech tools that are emerging from the confluence of the human genome project, advances in microcomputers and robotics are providing a quantum leap in knowledge and, more importantly, in the application of that knowledge. The pace is accelerating and, just like the moonshot, at least we now know what we're aiming for.

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