Personalised cancer therapies: why we may never reach the promised land

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New technologies offer wonderful possibilities for cancer patients. But the development of personalised therapies is being squeezed between the priorities of industry and a regulatory system that offers poor value for money. Is there a champion to clear a route to this revolution in treatment?

If society continues to cede responsibility for developing new generations of drugs entirely to the private sector, there is a serious danger that the potential of modern medical science to tackle diseases like cancer will never be realised. The wonderful possibilities new technologies offer for knowledge-based drug development – investigating the biological mechanisms of cancer, exploring ways of intervening in those mechanisms and learning to identify which patients require which combinations of therapies – will remain untapped. At best, we will remain in the situation we are now, with a steady trickle of expensive new drugs entering the market, often aimed at similar targets, with hardly any of the information doctors need to use them effectively.

This is the message Larry Norton, breast cancer specialist, former president of ASCO and member of the President's Cancer Panel under President Clinton, brought to the *Cancer World* media forum in Rome last October. It was delivered with the sense of urgency of a doctor who knows that the answers he needs to treat his patients correctly are within reach if only the research is done. Detectable too was a slightly weary sense of frustration of someone who, for years, has used his public status to make the case for greater public support for developing effective cancer therapies, and is disappointed by the lack of response.

If it is public response he is after, Norton might do better to point the finger of blame at the pharmaceutical industry – a popular target. Indeed he does not gainsay the many charges commonly levelled against it:

- drugs companies often set their sights low, seeking to add minor benefit to existing drug concepts rather than trying something really innovative
- many are averse to the paradigm of personalised medicine because it reduces the size of the market for each drug they develop
- their competitive structure leads to the duplication of much research and hinders urgent investigations into the potential benefit of 'cocktails' of combinations of drugs,
- a hefty mark-up for 'risk' adds significantly to the price of the final product, and
- doctors cannot use the product to good effect because the research to show how it compares with similar drugs and who benefits most has often not been done.

"But you can't blame the pharmaceutical industry for doing their job, which is to maximise profits for shareholders," says Norton. "The problem is the rest of society is not taking responsibility for curing cancer. By shifting the burden entirely to corporations, we have got what we deserve."

What we have got is a system that takes up to 15 years (see p18) and costs more than $800 million[1] to deliver a single new drug to market.

With such sums and time-scales, it is understandable that drugs companies avoid taking a gamble on highly innovative treatments. It is also hard to see how

developing personalised therapies for small subsets of patients can ever be economically viable under such a system.

There are many who share Norton's concerns. In an article published in 2004 in *Nature Drug Discovery,* Mike Rawlins wrote, "It increasingly seems that [the hopes of personalised medicine] will not be realized without dramatic changes in the way that new medicines are discovered and developed. The cost of drug development is so great that medicines are in danger of becoming unaffordable for either manufacturers to develop or consumers to purchase."

As Rawlins is chairman of NICE, the UK body that advises government and health commissioners on the cost-effectiveness of new medicines, his opinion counts. Indeed NICE has ruled against reimbursing the cost of many of the latest cancer drugs for patients in England and Wales, including cetuximab (Erbitux) and bevacizumab (Avastin).

Four years on, however, there is little evidence of the dramatic changes for which Rawlins was calling.

Shift the burden of risk

The problem is that the new knowledge-based drug development is far more time-consuming and costly than the try-it-and-see 'black box' model of the past. Yet the risk of failure seems much the same – the paradigm still holds that from 10,000 molecules screened, only 250 enter preclinical trials, 10 enter clinical trials and only 1 reaches the market.

Norton believes that investing significantly more public funding in the very early part of the drug development process would dramatically cut the costs to industry and encourage greater innovation. The public sector would accept more of the risk in this critical stage – discovering targets, developing 'lead' compounds that can be shown to have the desired biological effect, and looking at drugs derived from these lead compounds

ILLUSTRATION: STEVE DELL

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that preserve their activity with manageable toxicity.

Drug companies could then do what they do best: turning promising compounds into marketable medicines – altering molecules so the drug is more effective, more stable, easier to administer and suitable for large-scale manufacture, taking it through the regulatory hurdles, and determining optimal dose/schedule and the disease setting it works best in. "That's where competition should start among corporations – at a much higher level than it does now."

Shifting more early research into the public setting, adds Norton, could also reduce duplication. "One of the things that makes drugs expensive is that drug companies are often doing the exact same basic research, but not sharing the data or even sharing the fact that this research is going on. Once you start to divulge information about your research, it becomes no longer profitable to do secret research."

For those who are sceptical about this public funding approach, Norton points to the electronics industry "where most fundamental research in terms of semiconductors and computer development is happening publicly and is shared by everybody and the competition starts after you have the transistors. Who can build the better computer? That is one reason why we are making so many advances in computer science, because the competition starts at a much higher level than it does in drug development."

Norton is calling for funding for this very early stage of drug development to be doubled or trebled. "Only around 10% of meritorious grants currently get funded, and what you see is a dramatic shift away from innovation towards much more predictable research. It didn't used to be that way. For many years it was 20%, and if you get into the range of 30% of meritorious grants being funded, that's when you get to see exciting science."

Reduce the regulatory burden

Rawlins agrees that increasing academic involvement in the early stage of drug discovery will result in greater innovation. However, he believes that the main cost problem lies in a regulatory system that imposes a huge economic burden and takes almost no account of the barriers this erects to the development of new therapies. He wants to focus attention on cutting costs at the stages of preclinical safety tests and clinical trials, which, according the Boston Consulting Group, account for around 10% and 30% respectively of the cost of developing a drug.

Rawlins is a pharmacologist, who spent 12 years as vice-chair and chair of the UK Committee on the Safety of Medicines before taking over the chair at NICE. He recognises and welcomes the contribution that drug regulation has made to protecting society from a repeat of the thalidomide disaster and from drugs that are ineffective or manufactured to a poor quality. But he also recognises that patient groups with rarer diseases – which will also include 'subgroups' of more common cancers – pay a heavy price for this protection, because the added cost burden makes it uneconomical to develop drugs that could benefit them. That price, says Rawlins, is not taken into account by the bodies responsible for drug regulation.

In his 2004 *Nature Drug Discovery* article, he calls for "a full analysis and assessment of the mass of data held in the vaults of US and EU drug regulatory authorities," to establish whether these studies add sufficient knowledge to justify the added time and expense. "There needs to be a rigorous examination of the 'rituals' associated with drug development. Every step in the drug development pathway should be tested against two separate criteria: is there a clear evidence-base to support the continuing inclusion of the measure in the requirements of regulatory authorities? and does each regulatory requirement offer value for money?"

Preclinical safety studies can take up to three years and involve four types of investigation:

- the pharmacalogical screen (exploring potential effects of the drug on biological processes other than those intended)
- pharmacokinetic investigations of the drug in the species to be used for formal toxicology testing
- acute- and repeat-dose toxicology studies
- special toxicity testing such as mutagenicity, carcinogenicity and reproductive toxicity tests.

Rawlins raises a number of questions about the evidence base for many of these studies (see box). He queries, in particular, the value of conducting *in vivo* carcinogenicity studies on compounds that have tested negative in short-term mutagenicity studies, arguing that this either results in findings irrelevant to humans or reveals a tumour type that could be predicted from the compound's pharmacological properties. "If it doesn't damage DNA *in vitro*, but produces cancers in

Preclinical Testing:

DOES THE EVIDENCE JUSTIFY THE EXPENSE?

The pharmacalogical screen

- How strong is its predictive power?
- What is the basis for the safety margins used?

Repeat-dose toxicology studies

- To what extent are current regulatory requirements based on biological plausibility, rather than formal evidence?
- To what extent does 'target organ' toxicity, as identified in experimental animals, reflect likely toxicity in humans? What are the predictive powers?
- What is the real predictive power of repeat-dose studies lasting more than three months?
- What is the evidence base for the 'safety margins' assumed by toxicologists?

Special toxicity testing

- What is the evidence base for conducting *in vivo* carcinogenicity studies on compounds that have tested negative in short-term mutagenicity studies?

Source: Rawlins (2004), Cutting the cost of drug development? *Nature Drug Discovery* 3:360–364

animals, then the company toxicologists spend the next two or three years working out the mechanism of toxicology in the animals, showing that it wouldn't happen in a human being, so the whole study was a waste of time," he commented to *Cancer World*.

Rawlins accepts that the evidence base for the regulatory requirements for clinical trials is a lot stronger, but given that trials can take more than seven years to complete and account for a third of drug development costs, he believes that there is still a public interest case to investigate cheaper and quicker alternatives.

The current regulatory requirements are based on randomised, controlled, blinded, parallel-group clinical trials. But the methodology of drug development has changed dramatically since these requirements were drawn up. Today, the skill lies in a seamless process of gathering information about the drug and its biological effects in a variety of patients, disease settings, doses and schedules, from preclinical studies onwards, adapting each stage of the trial protocol according to the information gained from previous stages.

A variety of statistical methodological approaches – sequential, adaptive, decision-based and risk-based designs, as well as Bayesian techniques – have been developed to guide this process of scientific exploration. If these could be shown to be sufficiently reliable to provide the basis for evaluation for marketing approval, says Rawlins, the time taken to conduct clinical trials could be cut dramatically.

"We need to say what we really want to happen, and then develop regulatory processes around it," Rawlins commented to *Cancer World*. "At present, we do phase I studies, then ponder the results. Then we go to the regulatory authorities and ask to do a phase II, which takes another two years, and we ponder the results. We then go back to the regulators and ask for a phase III. We should move almost seamlessly from phase I to phase II to phase III.

"Why not have real-time regulation saying, for instance, 'We want to carry on the comparator group and we will carry on the mid-dose group and we will drop the high-dose and the low-dose group because the low dose doesn't work well, and the high dose is too toxic, and we now want to include more patients for the phase III.' We need that sort of approach. Then we could concertina the current six or seven years – we could halve it, or at least reduce it by one-third. Even if you can reduce the time it takes, that itself saves a lot of money, because of the time companies are spending money and not getting any return."

EMEA, however, is resisting using these types of statistical approaches as a basis for market approval. After a two-year consultation, EMEA published in March 2007 a report, Innovative Drug Development Processes, making it clear that 'Bayesian' methodology does have a place in drug development, but only for "hypothesis generating in earlier phases" and "the assessment of futility". With the possible exception of drugs for small populations, where an adequately powered

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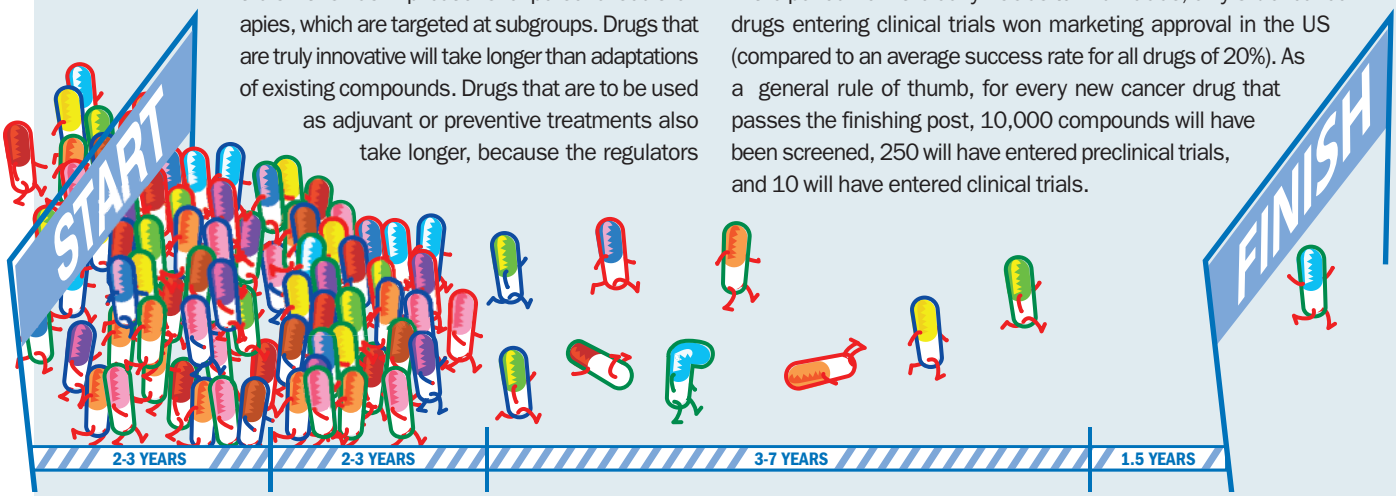
The long road to getting a new drug to market

It takes up to 15 years to get a new drug to market. Drugs intended for relatively small groups of patients tend to take longer than average, because it takes time to recruit sufficient volunteers to the clinical trials – this has implications for personalised therapies, which are targeted at subgroups. Drugs that are truly innovative will take longer than adaptations of existing compounds. Drugs that are to be used as adjuvant or preventive treatments also take longer, because the regulators require stronger data on safety where the drug is to be used in patients who may have no clinically evident disease. According to a report by the Tufts Center for the Study of Drug Development (2007), in the period from the early 1990s to mid-2000s, only 8% of cancer drugs entering clinical trials won marketing approval in the US (compared to an average success rate for all drugs of 20%). As a general rule of thumb, for every new cancer drug that passes the finishing post, 10,000 compounds will have been screened, 250 will have entered preclinical trials, and 10 will have entered clinical trials.



DRUG DISCOVERY	PRECLINICAL TESTING	SUBMIT CLINICAL TRIAL APPLICATION TO NATIONAL REGULATORY AUTHORITY	CLINICAL TRIALS			FILE MARKETING AUTHORISATION APPLICATION WITH EMEA	EMEA	
			Phase I	Phase II	Phase III			Phase IV
Cell lines	Laboratory and animal studies		20-80 patient volunteers	100–300 patient volunteers	1000–3000 patient volunteers			General patient population
Identify, prioritise and validate target. Select lead compound (compound believed to have potential to treat disease).	Does it reach the target? Does it have a biological effect? Is it safe? Can it be manufactured to a reliable quality – purity, stability, shelf-life?		What is the maximum tolerated dose of the drug? How does the body handle the drug? Are there any acute side-effects?	How effective is the drug in different cancers, used at the maximum tolerated dose? (Reject ineffective drugs at this stage.) What is the optimal dose? What side-effects?	Generate statistically significant data on efficacy and safety as the basis for applying for marketing approval.		Review process and approval.	Surveillance to keep a check on evidence of serious side-effects. Study new uses, patient types, long-term effects and different dosages.

"Those in charge of our public health cannot expect to get something for nothing"

phase III trial would be impossible, full phase III trials will continue to be compulsory, to "provide stand-alone confirmatory evidence of efficacy and safety".

Rawlins would like to see an international initiative to subject the whole issue to a 'value-for-money' analysis, based on retrospective reanalysis of a selection of past clinical trials, to see whether the approval decision would have come out any differently had a Bayesian approach been used. "It's perfectly feasible. It might cost a few million, and take two or three years, but that's nothing in the great scheme of things."

He believes the initiative would have to come from a European level, in conjunction with the US, and he has raised the general issue with the European Commission. He senses, however, that the Commission is reluctant to get involved in a major overhaul of the regulatory system, "because the next time a Vioxx happens – and it will happen – they would take the blame." (Merck's anti-inflammatory drug, Vioxx, had to be withdrawn from the market in 2004 after it was found to increase the risk of heart attack and stroke.)

But doing nothing to address the cost burden of regulation may kill off hopes of developing effective new personalised therapies. "If we do not work towards this goal, we will fail future patients, their families and society as a whole."

Regain control of clinical trials

Cost is not the only threat to developing effective personalised therapies. Perhaps the greater fear for Norton and his fellow oncologists is that they will never find out how to use the new drugs to greatest effect. Companies do not need to answer questions about which patients need what combinations of which therapies to get market approval for a new drug or to extend the indication for an existing one. Since the lion's share of funding for trials comes from the industry, industry can dictate the agenda. "It's the golden rule," says Norton, "The one with the gold makes the rule."

He says that the industry does not address the key questions that doctors want answered. "We are seeing an explosion of clinical trials that are company supported, and are designed to show that the drug has some merit, but not designed to try to influence in a productive way the standard of care."

These trials may, for instance, test a new drug A against existing drugs B and C, but not against the drug currently deemed to be the most appropriate for the relevant patient group, which is drug D.

"We call it a 'straw man' approach. We see dozens and dozens of trials like that, which are creating enormous confusion in my field, as important controls are being left out because they are not necessary to gaining regulatory approval. This is a tremendous dilemma for the practising cancer doctor. We are in a position where we have to make decisions about the treatment of patients where we don't know the answer. The thing that bothers me most is that we know the answer will never be found, because we know that the research needed to answer that question will never be done."

In fact, Norton is concerned that clinical trials are coming under increasing commercial pressure. In March 2007, he co-authored with Martine Piccart, Aron Goldhirsch and others, a Commentary in *Nature* entitled "Keeping faith with trial volunteers". They pointed to a growing trend for pharmaceutical companies to recruit academic investigators to conduct adjuvant trials in which the data will be controlled by the company outside the framework of a research cooperative group or a network of academic centres.

The authors warned of the dangers of allowing companies to control the research agenda in this way.

"First, if a trial is focused on answering a purely commercial question, vital opportunities to answer other important questions related to the care of patients and to biological understanding may be lost. Second, trial design can be distorted by commercial interest, for example, requiring an arbitrary duration of treatment, rather than focusing on the optimal treatment duration for patient benefit. We note an increasing tendency, especially in pharmaceutically controlled trials, to withdraw funding or cease follow-up studies after commercial endpoints have been satisfied...

"Data control entirely within a commercial organization may enhance the temptation to delay or suppress unwelcome findings. For example, large trials designed to define a subset of the patient population that benefit most from a treatment can run counter to the interests of a drug company wishing to maximize the number of potential patients for a new treatment. In such cases, control of data by the drug company would not be in the best interests of patients."

Returning to his earlier point, Norton emphasises that the pharmaceutical

industry cannot shoulder all the blame for this state of affairs. It is just another consequence of having shifted the burden of curing cancer entirely to corporations. He warns that a more equal partnership between the pharmaceutical trial sponsors and academic investigators will only happen if substantially more public money is made available.

An equal partnership

The industry itself is talking increasingly in terms of public–private partnership. The escalating cost of healthcare is prompting many European countries – and even the US – to look at ways of introducing some form of cost-benefit approach to reimbursement. Industry knows that what NICE has done in refusing reimbursement for many of its latest offerings, or at least severely restricting their use, is likely to spread. The companies have two options. They can work with academic researchers to demonstrate that their drugs really do represent value for money or accept that developing these drugs will become economically unviable. The pharmaceutical industry would prefer the former.

Most drugs companies now say they are keen to work in partnership with public health bodies to address the question of 'value in use'. Cynics may question their sincerity. They point to the failure of companies to carry out research to define which patient groups benefit most from new drugs, even when regulators specify this as a condition of conditional (early) approval – figures from the FDA show a compliance rate of less than 10%.

The industry attributes this largely to the difficulty in recruiting patients to trials of a drug that has already been approved.

Norton might add, however, that it is perfectly understandable that drugs companies may not want to sink resources into lengthy and costly studies that could well end up diminishing the market for their drug. Developing effective treatments for cancer is a public responsibility, and those in charge of our public health cannot expect to get something for nothing. If they want a say in how drugs are developed, they will have to pull their weight.

However, the industry also has a responsibility to make this partnership work. AstraZeneca's head of oncology, Brent Vose, accepts that companies have to change the way they work, and says he is sympathetic to criticisms of 'non-inferiority trials' (trials that seek only to demonstrate that a new drug is no worse than something already on the market).

He believes that patient stratification is very important here – breaking the trial population into groups to identify different levels of response according to, for instance, stage of disease or the presence/absence of a particular biomarker. "That is where this whole personalised healthcare, linking diagnostics with therapeutics starts to play out."

The key place to start doing this, he says, is in randomised phase II trials. "You have to come out of phase II with a hypothesis about the sorts of patients you want to take on. If you had choices you would obviously take those agents that did something better or in a different group than what already exists, because at the end of the day it is about patient benefit and about unmet clinical need."

He also accepts that companies need to take more responsibility for demonstrating the extent of benefit their drug offers across its intended patient population. Currently, formal assessment of what a new drug adds in terms of 'quality-adjusted life years' or similar measures of 'value in use' tends to be made after the drug has been approved. Vose would like to see data relevant to this collected within phase III of the clinical trial. "The whole quality of life agenda… probably needs to be played out in the trial design rather than as a retrospective data sweep up."

This is the point when doctors like Norton could start to get answers to questions about who really benefits from using the drug. And on this specific point too, Vose agrees that industry should do more. "When you start talking about targeted agents, the implication is that you target particular patients or particular stages of disease or particular combinations. The oncology community has to find out where that benefit is best placed. And it won't be sufficient for us to spend 30 years to find out how to use 5FU, because that is how long it took. That comes back to the need for close interaction between opinion leaders, investigators and companies about how we can find that benefit as quickly as possible."

Vose cites as one possible way forward a partnership approach in which conditional approval would allow the drug restricted use in certain public healthcare settings, where more could be found out about how many patients respond and who responds best, before the drug is allowed onto the market. "That would take you from hundreds of patients to thousands as quickly as possible, within a semi-trial situation. That seems to me to be a very good idea."

A proposal along these lines was made in the US during discussions about how to introduce the FDA's conditional approval procedure. The suggestion was that drugs approved this way would initially be used only in Medicare and Medicaid hospitals. But the idea was dropped and, currently, that research is simply not being done – as is evident from the 10% compliance rate with the post-approval studies demanded by the FDA as a condition of approval.

Who will champion drug development?

Norton, Rawlins and Vose come from the worlds of practising doctor and academic, drug regulator, reimbursement decision maker and industry. They may not agree about everything, but there is a

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shared understanding that drug development will have to change if it is to stand a chance of delivering on the great promise of personalised therapies. And there is clearly both the basis and the will for a constructive dialogue on how public and private players can work together to achieve that change. Yet there is also a real danger that the current unsatisfactory situation will just be allowed to drift, in the absence of leadership from government health departments, and the EU Directorate General for Health and Consumer Affairs (DG Sanco).

"We are dealing with a situation now when the funding available, compared to the opportunities, is grossly out of proportion," says Norton. Speaking to the situation in the US, where funding for cancer research has remained static for the last few years, he reels off figures to illustrate how little priority is given to finding ways to cure cancer. "The NCI funding, which is the entire funding for cancer research coming out of the US government, is a little above $4.5 bn. The total pharma investment for all diseases is about $50 bn, of which about 10% is cancer. US philanthropy is about another billion to billion and a half. Being generous, we are talking about $11.5 bn for all of cancer research for all cancers.

"In the same year, the American tobacco industry spent $16.1 bn on advertising and Americans spent $68 bn on soft drinks. If Americans didn't drink any soft drinks every Tuesday, and instead put that money in a pool for cancer research, we would be doubling the entire US budget for cancer research. If you go to any American and say: 'If I can dramatically accelerate the prevention and cure of cancer, would you be willing to give up drinking soft drinks one day a week?' they would say, 'Of course'. But we are not doing that."

The situation in Europe is worse. According to a report by the European Cancer Research Managers (ECRM) Forum published last September, Europe's per capita spend on cancer research from non-commercial organisations is only one-fifth of that in the US (up from one seventh, reported by the ECRM in 2005). Costs of clinical research, meanwhile, have escalated because of the badly thought out clinical trials directive.

More worrying, perhaps, is a trend for public funding for cancer research in Europe to speak primarily to the economic policy goal of making Europe a world leader in biopharmaceuticals, rather than the health policy goal of finding treatments for Europe's citizens. Instead of injecting a public interest goal into drug development, Europe's public money could instead be dragging existing academic research into the service of industry. This is a key concern flagged up in the ECRM report.

"EU money is often being partnered with industry and there is a real danger that if all increases in EU cancer research funding go this way, Europe's intrinsic creativity would be distorted by encouraging subsidy-seeking behaviour and essential areas of public health relevant to cancer, but not amenable to a business approach would remain orphans."

The ECRM warns against "priority-setting focused on predicted practical relevance, i.e. industrial utility."

The question is, who will champion prioritising a policy aimed at finding effective therapies for a disease that will kill one in every three European citizens? Who will argue the case for public money to be spent funding the sort of truly innovative approaches that could make a real difference in cancer treatment? Who will fight for the clinical research that may not deliver immediate economic growth and profit, but will give doctors the answers they need to treat the right patients with the right combinations of therapies – and will ultimately save vast sums that are currently wasted on treating patients with inappropriate therapies? Who will have the courage to initiate a review of the regulatory system that looks not only at the benefit of safety, but also at the obstacles the added costs pose to developing therapies for smaller groups of patients?

Norton tells an anecdote told him by an historian. "It's like the ancient Roman armourers saying to the ancient Roman senators: we know the Visigoths have burnt down the city and are about a block away from the palace, but how are you going to incentivise us to make swords?"

"The incentive," says Norton, "is that a third or a half of us are going to die from cancer. But we are not acting that way. We are acting as if this is a minor component of what we are doing."

1. The figure of $800 million to get one new drug to market is based on estimates developed by DiMasi et al. (2003) of the Tufts Center for the Study of Drug Development and a study conducted in 2001 by the Boston Consulting Group. Though the data behind these estimates are unverifiable, the figure is nonetheless widely used. The biggest criticism centres on the use of 'capitalised' costs, which include an estimate of what the money could have earned had it been invested elsewhere. It is, however, the capitalised cost that a company will consider when deciding whether or not to invest, particularly where the money is likely to be tied up for a very long time.