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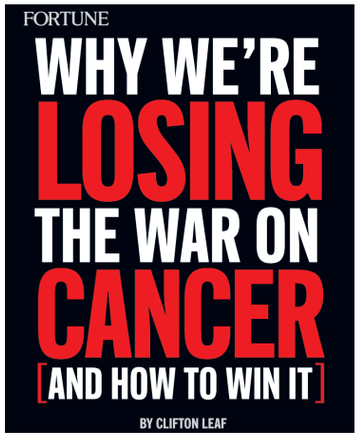
It's not a war... and we are not losing

Dispatches from the European front

Anna Wagstaff and Peter McIntyre

Thirty-three years after Nixon committed the US to defeating cancer, *Fortune* magazine talked to America's cancer gurus to find out what went wrong. The article makes depressing reading. But are things really that bleak? *Cancer World* invited leading members of Europe's cancer community to respond.

The estimated $200 billion spent on US cancer research since Nixon's National Cancer Act in 1971 has been largely wasted, and today, even controlling for age, "the percentage of Americans dying from cancer is about the same as in 1970 …and in 1950." This was the starting point of a damning indictment of progress in cancer treatment that appeared as a March cover story in *Fortune*, a leading US business magazine, under the title: "Why we're losing the war against cancer". Penned by the magazine's executive editor Clifton Leaf, the article analyses where it all went wrong and comes up with some controversial solutions.



What Went Wrong

• **Faulty models.** Researchers, he argues, work on mouse models that tell us little about the behaviour of tumours in human beings. Tumour shrinkage is accepted as the major indicator of a drug's effectiveness, but shrinkage has almost no effect on survival. Ninety percent of cancer deaths are from metastases, yet fewer than one in two hundred National Cancer Institute (NCI) grants go to research focused on metastases.

• **Regulatory straightjackets.** Slow and expensive clinical trials discourage drugs companies from taking risks and exploring radical approaches. With a time lag of 12 to 14 years and an average cost of $802 million to bring a drug to market, companies prefer to fiddle with existing compounds that buy a few extra months of survival. The system forces companies to test promising new compounds on the sickest patients, not on early stage cancer where a cure may be possible. It also hinders the development of cocktails of drugs aimed at multiple targets.

• **Dysfunctional cancer culture.** Leaf argues for a focused, collaborative effort aimed at finding a cure, arguing that it only took six years to develop the atom bomb, and eleven to land a man on the moon. Instead we

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BETTMANN / CORBIS / CONTRASTO

President Nixon signs the National Cancer Act, 23 December 1971, giving him personal command of a $1.6 billion effort to find the causes and cures of cancer, which had killed 325,000 Americans that year.

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have fragmented research, characterised by destructive competition and rewarding publication that contributes little to curing cancer. The legal, regulatory, academic and institutional systems combine to obstruct the development of multi-target compounds that are the most promising way forward.

How to win

Leaf sets out his prescription to win the war on cancer.

- Remove legal and regulatory constraints and give drug companies incentives to test cocktails of experimental drugs in shorter trials.
- Shift resources from advanced cancer towards detecting those at risk and treating pre-cancerous lesions before they turn into cancer
- Test drugs on people with less advanced disease.
- Transform the drug approval system.
- Move towards a funding culture that favours cooperation and focus on the big picture.

These arguments are not new inside the oncology community. Epidemiologist John C Bailar argued in the *New England Journal of Medicine* in 1986 that "some 35 years of intense effort focused largely on improving treatment must be judged a qualified failure," and in 1997, "we see little reason to change that conclusion, although this assessment must be tempered by the recognition of some areas of important progress."

He said: "Prudence requires a sceptical view of the tacit assumption that marvellous new treatments for cancer are just waiting to be discovered," and concluded that there was a pressing need to re-evaluate research strategies and to put more money into learning how to do prevention effectively.

In 2002 in the *British Medical Journal*, Italian pharmacologists Silvio Garattini and Vittorio Bertele alleged that new anticancer drugs reaching the European market between 1995 and 2000 offered no substantial advantages over existing drugs but cost many times more. They concluded: "there is little to justify some of the promises made to the public."

The *Fortune* article took such arguments to a broader arena, raised the level of polemic and included the new generation of targeted drugs in its sights. And in place of the "cancer breakthrough" stories it has run in the past, it flagged up more and quicker trials of cocktails of experimental drugs at an earlier stage, and mass screening, as the new way forward.

But are we losing the war on cancer? And are more clinical trials combined with a programme of mass screening really the panacea? *Cancer World* posed this question to leading figures from the European cancer community, and asked what they feel are the major obstacles to progress and the key changes they would like to see.

The view from Europe

Our sample of 14 experts was drawn from the worlds of clinical treatment, research, regulation, pharmaceutical industry, nursing, and patient advocacy. They represent, without doubt, the voices of experience.

Every one could give a masterclass on the daily struggle with cancer, each coming from a different perspective. But from behind this diversity of viewpoints and insights there emerges a consensus about the nature of the problem that allows conclusions to be drawn about where Europe should be focusing its efforts.

The first area of agreement is that cancer is massively more complex than any known disease including HIV. Trialling as many combinations of unproven compounds as possible in the hope that you 'strike lucky' is therefore unlikely to prove successful.

The second is a sense of confidence that increasing knowledge about the genetic origins and mechanisms of cancers will eventually translate into effective methods of control: we know where we are going, and have some idea of how to get there. However, the idea that we already know enough to identify the early stages of cancer through mass screening programmes, or know how to respond to danger signs, is wide of the mark.

Professor Mariano Barbacid of the Centro Nacional de Investigaciones Oncológicas (CNIO) in Spain

EPIDEMIOLOGIST

Peter Boyle

Director of the International Agency for Cancer Research, France

■ The significant progress in reducing mortality from cancer has virtually all come from public health interventions.

■ I know how to save 400–500,000 deaths per year in Europe. You just stop people smoking today.

■ As a society, I think we fund too much very basic biological research under the disguise of cancer research.

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ONCOLOGIST

Jonas Bergh

Professor of Clinical and Molecular Oncology, Radiumhemmet, Stockholm, Sweden

■ The search for accurate therapy-predictive biomarkers and surrogate markers should be given highest priority. We need screening methods that are rapid and cheap so you can screen large populations to find the very few who will benefit from therapy.

■ We need more biopsies of metastases. They may be dissimilar to the primary tumour, which may affect treatment selection.

■ Extensive collaboration is needed within the industry and acadaemia, because cancer is heterogeneous with multiple genetic alteration and needs to be hit with multiple drugs hitting multiple targets with an individually tailored therapy strategy.

summed up the feelings of many about the solutions proposed in the *Fortune* article: "…some of them are impossible; some are unethical and some are just difficult and don't work. If we were to implement them we would be worse off than we are in today's world."

However, many of our experts expressed sympathy with the general concerns in the *Fortune* article. There is a worry that many of the new drugs hitting the markets bring scant benefits at a cost to public health systems that could prove unsustainable. Many experts believe there is much to be done to improve the effectiveness of research. Serious questions were also raised about whether some of the money spent on new drugs might not be better spent improving the quality of Europe's cancer services, from prevention, screening and early diagnosis to treatment and palliative care.

There is clearly a debate to be had – one that requires the voices of patients and the public as well as experts. The views presented in this article are an important contribution to this debate. We hope it will encourage more people to join in.

Winning or losing?

Our team of experts agreed that in order to evaluate our progress, or lack of it, in controlling cancer, we need to understand what we are dealing with. First of all, cancer is primarily a disease of the elderly, and because people are living longer than they used to, cancer rates are going up. In effect, cancer statistics suffer from improvements in the general health of the population resulting from better prevention and treatment of fatal conditions such as heart disease and stroke. To characterise this as a failure, argues Barbacid, is like arguing that "medicine in the 20th century did not improve because the same number of people are dying – which is 100% of them."

The second point of agreement is that the 150–200 diseases collectively known as cancer are astronomically complex. Tumours look the same but have a different molecular structures in different people. Five, ten or more oncogenes may mutate in different ways according to rules we do not yet understand. Tumours are masters of adaptation with an ability to stay ahead of the chasing pack.

As Professor Mario Dicato from the Centre Hospitalier in Luxembourg puts it: "The whole biology and genetics of cancer is like a crime story. The cancer cell is a fantastic Darwinian model. The cancer cell does not have to respect anything in the hierarchy of cell organisation. Normal life is about aging but cancer just promotes its own immortality."

And so breast cancers, for example, metastasise into the bones and other organs, effectively becoming completely different tumours. Looked at from that perspective it becomes easier to see why the longed-for "cancer breakthrough" has evaded us for so long.

And yet the story told by the statistics is one of steady progress in controlling

PATIENT ADVOCATE

Lynn Faulds Wood

Founder of Lynn's Bowel Cancer Campaign, UK

■ There's no question that we would save most lives if we focused on prevention, but there's no money in it. All the money is at the wrong end of the disease.

■ I would introduce flexible sigmoidoscopy for colorectal cancer, and I would also sing out loud to the nation the benefits of walking.

■ Give us genuine information about costs, benefits, side-effects and quality of life.

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CANCER NURSE

Nora Kearney

Professor of Cancer Care, University of Stirling, Scotland

■ We have to start involving those whose voices wouldn't normally be heard. …We need to say: this is the resource we have – if you want to do mass screening for cancer, we can't treat heart disease. …We need to start this dialogue.

■ We need to sit down – as scientists, clinicians, regulators and industry – and sort out our priorities, pool our resources and start work on those collaboratively.

■ [The war analogy] led to a very close focus on cure, rather than prevention, supportive care, the process of the illness and how to manage it.

cancer – slow for some tumours, faster for others.

Professor Gordon McVie, of the European Institute of Oncology, Milan, points to figures from the UK showing that five-year survival rates in breast cancer have improved by 24% in the last 12 years, and in England and Wales mortality figures for all cancers together have shown improvements for each successive five-year period for 25 years. "That doesn't sound to me like losing anything."

It all adds up to around a 12% decrease in deaths from cancer over the past 20–30 years, according to Dr George Blackledge, Clinical Vice-President of AstraZeneca. In the face of the increase in people being diagnosed with cancer, he said, "it is actually rather encouraging."

What the statistics don't show is how much of this progress is due to prevention, screening and early detection, and how much is down to improved treatment.

Professor Peter Boyle, an epidemiologist who heads the International Agency for Cancer Research (IARC) in Lyon, puts the decline in cancer rates in Europe almost all down to public health measures, particularly tobacco cessation, with cervical and breast cancer screening also playing a role. He points to last year's review of the Europe Against Cancer Programme, which found a 9% drop in the number of people being diagnosed with cancer compared to 1985. He gives scant credit to improved medical therapies. "There has been no significant breakthrough in treatment in the past 30 years, since cisplatin was introduced for testicular cancer," he says.

His views are partly borne out by the experience of Nora Kearney, a Professor of Cancer Care at Stirling University. As part of her research, she recently returned to clinical work on a part-time basis, and says she found that little had changed. "It's terribly disappointing to come back after 12 years only to find that we are still giving largely the same regimes for most of the common tumour types."

Yet while the high hopes for a series of rapid breakthroughs that followed the introduction of drugs like cisplatin and the MOPP regimen for non-Hodgkin's lymphoma have faded, many experts warn against dismissing the progress that has been made through the cumulative effect of little steps.

This is the case made by Professor Jonas Bergh, a breast cancer specialist at Stockholm's Karolinska hospital. "If you use tamoxifen for 1–2 years, you have a survival gain in receptor-positive patients, if you use it for five years you have further gain. If you use CMF chemotherapy you have a survival gain, and if you add in anthracycline you have a further small gain. If you add taxanes you very likely have a further gain. Here you have small steps which together lead to a mortality reduction in the order of 30% or 40%."

Dicato says he is sceptical about the

ONCOLOGIST

Gordon McVie

European Institute of Oncology, Italy

■ I can't think of a more exciting field for a young person to go into than cancer research at the moment. It's absolutely bursting out all over.

■ I'd start with intelligent people and a career structure that is attractive to getting the brightest brains into the area of cancer research – people with completely different skills from the present generation of cancer researchers.

■ Biotechnology companies are a totally neglected area in the [*Fortune*] article. If I had any extra money, this is where I would put it.

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value of "another fancy drug" on the market, but he too points to steady progress. "We have more than doubled the median survival in colorectal metastatic cancer over the past ten years, from around 8–10 months to something like 20–25 months. It would not be preposterous to say we will double it over the next ten years, to 50 months. It will continue to be small steps because since Lourdes there have not been many miracles."

One of the steps in this story has been the use of Erbitux [cetuximab] which, says Dicato, when used in combination with an older drug, has shown a response in 30–50% of patients with advanced metastatic disease.

And although Blackledge from AstraZeneca agrees that early detection is the key to successful treatment in many cancers, he insists that drugs also play their part. "There are probably 600,000 women alive in the world today who would otherwise be dead if it were not for tamoxifen.

"I think Mr Leaf has quite some cheek in writing such a pessimistic paper [the *Fortune* article] because he was treated and cured for Hodgkin's disease using exactly the techniques that he criticises so strongly. It is not one or two cases, it is tens of thousands of people who have been truly cured and certainly hundreds of thousands of people who have had their lives extended."

More important than whether the glass of past progress is half empty (far slower than we had hoped) or half full (steady progress through small steps) is the question of how our experts see the future. On this question there seems to be not just a consensus, but a real excitement that our ability to identify the genetic mutation responsible for individual tumours will, in time, enable us to develop effective targeted therapies.

Even Boyle, who is the most dismissive of past progress in drug therapies, is upbeat. "We are entering a wonderful new phase, with marvellous technologies and innovations, focusing on genetic defects. I'm very hopeful these will turn into new magic bullets for certain types of cancer."

Glivec (imantinib) is one of the most well-known of the new generation of targeted drugs. Developed and brought to market for chronic myeloid leukaemia (CML), it proved so effective that its approval had to be rushed through under massive pressure from patients and clinicians. Since then, it has been shown to be effective in a rare stomach cancer, gastrointestinal stromal tumour (GIST), for which there are few alternative treatments.

Glivec was dismissed in the *Fortune* article on the grounds that CML is an unusually non-aggressive and simple cancer, and anyway some tumours had developed an immunity to its effects.

None of our experts accepted these arguments. Barbacid, who was involved in the discovery of the first oncogene, and has particular expertise in the area of targeted treatments, argues that whether CML is aggressive or not is neither here nor there. The point is that the drug targets the gene that causes it, and that gives hope for the future. "This is the first example of therapy of a cell molecule that blocks the action of a specific oncogene."

Iressa (gefitnib) is another drug that shows that targeted therapies can be extremely effective. The drug was developed for patients with lung cancer, and early on there were doubts about its effectiveness (which were highlighted in the *Fortune* article).

This is a drug about which Barbacid had severe doubts. It was developed, he says, against the EGFR (epithelial growth factor receptor), and there was no evidence that this mutated in lung cancer. However, after the drug showed benefits, it was discovered this year that a small percentage of lung cancers do have mutated EGFRs. "Iressa is a wonderful story," says Barbacid. "So far there is a perfect correlation between response to the drug and the mutation."

Glivec and Iressa form part of a growing evidence that targeted therapies can work, and that increasing knowledge about the genetics and cellular mechanisms of tumours will in time transform survival rates. The question

REGULATOR

Isabelle Moulon

Head of Safety and Efficacy of Medicines, European Medicines Agency (EMEA), UK

■ Things are moving on. We need to look at different sorts of drugs, we need to look at different designs, different end points, surrogate markers, biomarkers, and take all these things into account.

■ If it is proven that a biomarker is a good marker of survival… we will accept it. We have already done that in the HIV field.

■ We need more coordination between the work of research, industry and the regulators… on where we want to go and how we want to get there.

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Ten suggestions for improving cancer control in Europe

THE OBSTACLES THE SOLUTIONS

1

Europe has paid only lip service to prevention. Efforts remain limited and often ineffective.

Focus more attention on prevention – the single biggest factor behind the drop in cancer deaths in past decades. Invest in research to show what works best. Target prevention programmes to specific groups and sharpen the messages.

2

We have no way of screening effectively for the majority of cancers.

Prioritise search for effective screening methods and introduce more high-quality programmes where they are known to work.

3

The public and patients are poorly informed which can delay diagnosis and make it harder for patients to live with their disease.

Educate the public about risks and symptoms. Promote an understanding of cancer as many diseases, most of which are chronic and can be managed using a variety of treatment options. Offer patients information, tailored to their needs and preferences, to allow them make informed decisions about treatment options, some of which offer a difficult choice between potential extra survival and quality of life.

4

Market pressures can be poorly aligned with clinical priorities. A risk-averse pharmaceutical industry has little incentive to look for innovative treatments that make a radical difference. It focuses on the most common cancers and the biggest markets. Rarer cancers, including paediatric cancers, can be overlooked. There are commercial and legal barriers to testing drugs in combination. The demands of commercial confidentiality lead to wasteful duplication.

The industry, academic researchers, clinicians, and regulators need to get together and discuss, in a public and transparent dialogue, how to work together to develop effective drugs more quickly. Full publication of the results of both positive and negative clinical trials should be mandatory. The industry should be encouraged by a combination of incentives and regulation to test promising drugs in rarer cancers (which in the new world of tumour genetic profiling, may eventually include all tumour types).

5

Research models are inadequate.

Clinicians, academic researchers, regulators and the industry should seek to agree on a way forward. Possible priorities include finding: better models than fast-growing single-gene tumours in mice; pre-signs of cancer that open new opportunities for screening; biomarkers that predict survival better than tumour shrinkage, and targets in primary tumours and metastases that may respond to new therapies.

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6

Clinical research in the academic setting, where it is easier to collaborate and focus on clinical priorities, is stifled by bureaucracy, exacerbated by the EU's Clinical Trials Directive. It is hard to get patients to join trials. State funding for cancer research is concentrated in basic science rather than clinical research. The European research effort is too fragmented and nationally focused.

Increase and coordinate public and charitable funding for clinical multimodality research. Reduce the burden of bureaucracy. Monitor the impact of the EU's Clinical Trials Directive and press for an early rethink. Let patients know what clinical trials are happening and where. Explain to patients what each could gain from participating. Work towards a single European cancer registry and a Europe-wide approach to research.

7

People are dying unnecessarily due to inadequate cancer care. Non-specialist surgeons in general hospitals too often fail patients.

Concentrate treatment in specialist settings using a multidisciplinary approach covering surgery, radiotherapy and drugs. Spend money on setting high standards for clinical care and bring all practitioners up to these levels. Ensure that complicated cancer surgery is performed by surgeons with the required expertise.

8

Existing knowledge and techniques are not disseminated effectively.

Invest in translating knowledge into practice and provide continuous updates for doctors and nurses.

9

Research will be stifled if it fails to attract the best young scientists of the future.

Encourage a new generation to enter cancer research with skills for the new era of genomics. Offer good career structures. Select people by interview and peer review rather than by their publication record.

10

We can't do everything. If we invest more public money in clinical research we may not be able to fund increasingly expensive drugs for a growing number of patients. If we reshape services based on specialist cancer centres we may not be able to fund every new screening programme.

These are priorities only the public has the right to decide. We need an open, inclusive and well-informed debate about options and their implications. *Fortune* raised these issues among its elite American readership. We must find ways to promote the debate across all levels of European society.

What do you think? Where should we concentrate limited resources? How do we present the issues to the public and stimulate debate? Send your suggestions, views and comments to the Editor at editor@esoncology.org, and we will publish them in a future issue.

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ONCO-HAEMATOLOGIST

Franco Cavalli

Istituto Oncologica della Svizzera Italiana, Switzerland

■ Winning the war on cancer would mean that we know almost everything about the most hidden secrets of life.

■ There is no other field of medicine where cooperation is so well structured as in cancer.

■ I think [regulators] have set the bar a bit too low. If you set the bar a bit higher, then you will oblige the pharmaceutical companies to develop research to come up with significantly better drugs.

is, as ever, how much time? And is there anything we can do to speed up the process?

Obstacles to progress

We asked our European experts what they saw as barriers to faster progress, and in particular, whether they agreed with the cited problems of faulty models, lack of collaboration, heavy-handed regulation and a dysfunctional cancer culture.

Their responses generally reveal frustration that such a large proportion of cancer research is in the private sector, where barriers to sharing information and collaboration are greatest. Pharmaceutical companies have much less incentive to develop drugs for rare cancers – or indeed for small sub-groups of patients within the major cancers. Interestingly, the drugs companies acknowledge difficulty in reconciling their commercial imperatives with clinical research priorities. Many of the other challenges cited are common to the academic researchers, the industry, regulators and clinicians alike; such as identifying new biomarkers, finding more effective ways of testing drugs, testing combinations of targeted drugs, and increasing public understanding about the nature of cancer and cancer treatments. There was a feeling that in these areas at least there could be great scope for working more closely together.

COLLABORATING IN THE LABS

The need to improve collaboration was widely accepted – but not everyone agreed on the main obstacles.

Boyle, who as head of the IARC is trying to bring together the directors of the world's national cancer institutes to reduce duplication in clinically oriented research, believes that fragmentation of the European cancer research effort is a major problem.

"If the NCI decides to create a huge proteomic centre for the US, they'll put big investment into it, and they'll get the best people and they'll set the thing up. If Europe decided to do that, we won't have one European proteomic centre, we'll have a small one in the UK, a small one in France, and a tiny one in Greece and so on. While the US benefits from having a population of 250 million to draw the best experts from at national level, in Europe we have a population of 500 million, but we don't have the impact, because we think like a series of different countries."

He believes that the recent establishment of a European Research Council, and the possibility of a European Medical Research Council, are steps in the right direction. "This will reduce the fragmentation in how government research money is spent. But it won't apply to national charity funds, which accounts for most of the research money. We still won't have the same pot of money available to every researcher in Europe, as they have in the US."

However, McVie, who until recently was head of the UK Cancer Research

PHARMACEUTICAL EXECUTIVE

George Blackledge

Clinical Vice-President of AstraZeneca, UK

■ Last year we did more than 150 deals with other companies to work together to deliver newer treatments and look at combinations of treatments.

■ Mr Leaf has quite some cheek writing such a pessimistic paper because he was cured of Hodgkin's disease using exactly the techniques that he criticises so strongly.

■ We believe in attacking the disease at an earlier stage, but you have to do it in a safe way because you could damage a lot of people if you get it wrong.

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PHARMACOLOGIST

Giovanni Apolone

Head of the Laboratory of Translational Research, Mario Negri Institute for Pharmacological Research, Italy

■ If you spend too much money on this kind of drug you do not have money to increase the numbers of good physicians able to give the best treatment to patients.

■ I agree with the general message of the [*Fortune*] article. Our capability to cure or postpone the death of people with metastasis is very poor.

■ We have to educate people that there is no magic way to cure such a complex disease and most new drugs are no better than the old ones.

Campaign, says allegations of a fragmented cancer effort are completely out of date. "Today all the major cancer research players in the US and the UK enter details of their projects on a single database, and hopefully the same will soon apply in Europe and Japan. You can go to the database and see what is happening to a particular kind of research – say metastases research in sarcoma – anywhere in these countries."

The real problem, argues McVie, lies within the industry. "The only people who still don't want to collaborate and let other people know about their research are the drug companies. The pharmaceutical industry spends $6 billion on research and development in the US alone, and we know very little about how this money is being spent," he says.

Dr Giovanni Apolone, who is head of a translational research laboratory at the Mario Negri Institute in Italy, agrees that the failure of drug companies to share their full results leads to redundancy in research. "Sometimes they have spent so much money on a given drug that at the end, even if they realise it does not have a new ability to control cancer, they keep going because it is better to have the drug on the market than not. Regulatory agencies receive the information they require to make a decision. It does not mean that the companies give regulatory bodies or the public everything the company produced over ten years. There are efforts to force pharmaceutical companies to make available to researchers and the public all the studies, but most countries give companies a right not to give information to competitors."

Blackledge from AstraZeneca says that companies do collaborate.

"Last year we did over 150 deals with other companies to access their technology and indeed to work together to deliver newer treatments and look at combinations of treatments.

"It is a question of when you start to collaborate. When you are actually finding out about a new molecule which may become a useful new drug there is a lot of work to do. We ought to make sure that it is as safe as it possibly can be and we need to do that in isolation from other things. Only then can we combine that agent with another agent. It would be irresponsible and dangerous to do anything else."

Dr Bernhard Ehmer, Leader of the Oncology Business Area at Merck, Germany, agrees that it would be good to see more collaboration between pharmaceutical companies, but points out that the legal questions of ownership and liability are very hard to resolve. He suggested that there should be more collaboration between the industry and public research institutes, acadaemia, health authorities and health insurance funds. This could be one way, he suggested, to help pharmaceutical companies overcome bureaucratic hurdles to collaboration – such as the legal issues that hinder joint research.

Ehmer shares some of the critics' concerns over revealing information. "There should be more sharing of data, including negative data," he says. "Very often you see data of experimental drugs, you only see the positive data as the negative data are not published by journals or accepted for presentation at scientific meetings."

Apolone believes that pharmaceutical companies and public institutions could work in tandem with a different responsibility for each sector. "A lot of money should be put into public and academic research to pick up promising drugs as soon as possible and study them in the public domain. The companies should demonstrate safety and activity and then comparative trials where new drugs are compared with the old ones could be done with public national institutions in conjunction with pharmaceutical companies. This would give more solid data before marketing the new drugs."

Not everyone agrees that pharmaceutical companies are the only ones who have trouble collaborating. Kearney, who has spent years conducting studies in cancer nursing, says that competition between academic institutions also works against attempts to collaborate. "To get a grant", she says, "I have

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to show certain levels of 'returnable outputs', such as having my name as first author on a paper. When you work collaboratively, this doesn't always happen. Most of my research has been done collaboratively, and this fact alone almost doubles the time it takes to write a grant proposal."

She argues that there is a tremendous amount to be gained from getting scientists, clinicians, regulators, and the industry to sit down together and try to agree priorities for the next five years.

Others defended the collaborative record of cancer researchers. Professor Franco Cavalli, of the Istituto Oncologica della Svizzera Italiana, Bellinzona, Switzerland, accepts that universities find themselves under increasing pressure to patent new discoveries and compete, but argues that cooperation in cancer research is the envy of every other field of medicine. "The idea of cooperative groups arose in the field of cancer. There are national, international, continental cooperative groups and there are intergroup studies." The problem is funding. "Thirty years ago most drugs were developed in public laboratories, where cooperation is easier. Today, the state is pulling out of research and leaving it to pharmaceutical companies."

Stella Kyriakides, President of Europa Donna, the European Breast Cancer Coalition, says that the Breast International Group (BIG) is breaking down barriers. It helped to form the TransBIG group, funded by the European Commission, as a research network of 40 partners from the EU and Latin America that aims to develop tailored adjuvant treatment for breast cancer patients. Europa Donna has been accepted into partnership and given the critical task of disseminating research information through its national bodies and ensuring that women are better informed about clinical trials.

Kyriakides said: "The effort to involve institutions of many countries at a very high level of collaboration will hopefully stop this fragmentation so that they will bring individualised treatment to breast cancer patients earlier. I think it is a great success that Europa Donna, as an advocacy organisation, is a partner in this group."

McVie has concerns about other aspects of what *Fortune* called the 'dysfunctional cancer culture', in which academic qualifications and prestige publication become more important than the ability to innovate. This could limit our ability to exploit the latest knowledge and technologies. "My major concern about cancer research is not that it's not delivering – I think it is delivering. The question is whether it is going to deliver in the next 10–20 years. I think that the main stumbling block in the future will be the human resource. We are not breeding the right kind of bright young person to go into cancer research.

"I think the cancer culture, group think, the cliquiness of the grant system has something to do with it. The idea of measuring academic achievement by publication record over all else is a fact, and I think it is terrible."

MODELS AND MEASURES

If the issue of culture and collaboration within the cancer community exposed fault lines between its separate components, all our experts found common ground in their frustration with the mouse. No-one, it would seem, wants to continue to base the strategy for developing new drugs on what works in mice. However, no-one has come up with a better alternative.

Kearney hopes that a greater understanding of genetics may allow a move from the mouse towards genetic modelling, but points out that there will always be a need to test drugs for toxicity: "You can't just test untried drugs on human beings."

Barbacid argues that bypassing the mouse would increase the number of drugs that are tried out on humans. "Right now there are more than 430 drugs in clinical trials. What would happen if [mouse tests] were removed. How many would we have – 2000 drugs?" However, he agrees that the mouse model may be developing the wrong drugs. "Many drugs cure

BASIC RESEARCHER

Mariano Barbacid

Director of the Centro Nacional de Investigaciones Oncológicas (CNIO), Spain

■ Cancer is more than 150 diseases. So long as we continue to define cancer in the singular it is very difficult to communicate to lay people about the diseases.

■ One could argue that medicine in the 20th century has not improved because the same number of people died in 1900 as in 2000 – 100% of them.

■ Iressa is a wonderful story… nature has demonstrated a perfect correlation between a mutation that causes cancer and a response to a drug.

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PHARMACEUTICAL EXECUTIVE

Bernhard Ehmer

Leader of the Oncology Business Area for Merck, Germany

■ If someone says we lost the war against cancer, that is premature. In the past we did not understand a lot. Only now are we in a position to attack it more precisely.

■ The development of new drugs is very slow and extremely expensive. We have to show the safety and efficacy of each component. I agree that this encourages pharmaceutical companies to be risk averse.

■ There should be a more open sharing of data, including negative data. Very often you only see the positive data and the negative data are not published.

human cancers in mice but when they go to human patients they do not do the same. They kill fast growing tumours but lung cancer can take 30 years [to develop]."

Ehmer agrees that the mouse model, which is integral to Merck's drug development work, is not ideal. "The question at the end is what conclusions do you draw? For us that is one methodology to obtain a set of data but we do not draw all our conclusions from that."

Leaf's argument that we are concentrating too much effort on late stage tumours, where the chance of a cure is very small, also met with a lot of sympathy as a basic research principle – but as Dicato points out, we need a cure for real patients, and most of them are diagnosed at a late stage. Both McVie and Boyle, however, think the charge is unjustified and out of date. They point out that an explicit focus in the US National Cancer Institute's '2015 challenge' is to try to stop the evolution of the disease at each stage "from the initial event to the preclinical event, the postclinical event and the metastatic progression."

There are also mixed views on whether we are relying too heavily on tumour shrinkage to measure a drug's effectiveness. McVie believes this charge too is out of date. The regulators who decide which drugs get approved (the Food and Drug Administration in the US and EMEA in Europe) now actively encourage drug developers to look for new biomarkers and surrogate end points that are more accurate predictors of survival," he says.

However, Apolone, who sits as an expert on EMEA's efficacy working party, says that about 50% of new drug indications submitted to the FDA last year were based on tumour shrinkage, and that the situation in Europe is similar. When the drug that shrunk the tumour is used in clinical practice "you are rarely able to see any clinically meaningful difference", he says.

Bergh believes there is far too much of a focus on shrinking tumours. "Tumour shrinkage studies cannot address the issue of the heterogeneity and constant mutation of tumours. We need to use biopsies and PET [position emission tomography] investigations to see what is really happening in the tumour. We are far too conservative at taking biopsies from metastatic lesions. Everyone takes for granted that the metastatic lesions are the same as the primary tumours, despite the fact that there are very few, if any, studies systematically studying whether this is the case."

Professor Jacek Jassem, who is Head of Oncology and Radiotherapy at the Medical University of Gdansk, strongly agrees with this approach.

RADIATION ONCOLOGIST

Jacek Jassem

Head of the Oncology and Radiotherapy Department at the Medical University of Gdansk, Poland

■ The majority of patients everywhere in the world are treated with local therapy, surgery or radiotherapy. Many receive pharmacological therapy as part of the treatment, but this is not the main approach.

■ Clinical research sometimes focuses too much on a surrogate endpoint, like response. We have to change our approach by putting more emphasis on real benefits for the patient.

■ Biological differences between tumours is an attractive and promising area of research. It is not much supported because the pharmaceutical industry want to treat all patients rather than selected patients.

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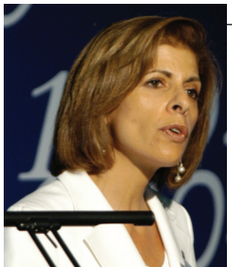

PATIENT ADVOCATE

Stella Kyriakides

President of Europa Donna, the European Breast Cancer Coalition

■ We know that where we have early detection there is a better survival rate for women.

■ We are losing lives that could be saved because many European countries do not have screening programmes and state of the art treatment centres.

■ I think it is a great success that Europa Donna is a partner on the transBIG consortium bringing together 40 research centres from 21 countries.

"We do large clinical studies to detect a very tiny difference between two therapies. I think we should focus more on biological differences between the tumours that give us suggestions that one therapy might be much better in this particular tumour than another based on this biological or molecular marker. This is an area of research which to my mind is very attractive and very promising, but is not that much supported by the industry because they want all patients to be treated with new drugs rather than selected patients."

Not everyone is so dismissive of tumour shrinkage. Blackledge argues that "It is a great start. By and large once you start shrinking tumours you know you have got something that is of potential benefit." But in the end, he agrees, drugs are measured by their ability to affect the time until the cancer comes back, quality of life, and survival. Cavalli agrees that shrinkage is a significant measure. "It is true that most people die from metastases, but in most tumours, shrinkage of tumour goes in parallel with shrinkage of metastases. We can measure shrinkage of the tumour much more easily than shrinkage of metastases, which sometimes we can't even measure by PET scan."

THE REGULATORY STRAIGHTJACKET

If there was one culprit singled out by the *Fortune* article for blame over the lack of progress in new treatments over the past years, it was the clinical trials system overseen by regulatory authorities.

The system is slow, expensive and inflexible, argued the article, which deters drugs companies from taking risks, or innovating with cocktails of experimental targeted drugs in early disease.

Ehmer, from Merck, says "We must be very honest, initially we mostly go for incremental improvements because of the regulation and the costs of long and risky clinical development. We like to see increased efficacy or a better safety profile in advanced disease before we embark on studies with new combinations or in earlier disease." He points out that regulators usually ask the companies to prove the usefulness of each ingredient in a trial of a cocktail of drugs, even though it may only be the combination that proves effective.

Dr Isabelle Moulon, from EMEA, says that effective multi-target treatments for HIV were developed under the same regulatory system. She believes that recent changes in European approval procedures have introduced as much flexibility as is consistent with the public interest. Cancer drug approval in Europe is now channelled through a single agency (EMEA), and a number of fast-track procedures have been introduced. These include accelerated approval where a drug is very promising, early approval for "compassionate use", and conditional approval for use in a life-threatening disease, where a drug has been shown to be safe. EMEA has started discussing and exchanging information with the FDA in order to streamline companies' development programmes and the approval process. Moulon points out that EMEA has set up expert advisory groups for all the new technologies and says drug developers are now encouraged to discuss designs early in the process. But she insists that public safety must come first. "You have to remember where we came from. It was the catastrophe with thalidomide that led to the first European law on regulation.

"Most of the products used in cancer are still very toxic and we need to be careful what we do to patients."

In addition to such ethical problems, the slow time to robust results, and commercial and legal obstacles to collaboration between companies, tended to be cited as the real obstacles to Leaf's strategy of testing cocktails of unproven drugs on early-stage cancers.

SERENDIPITY

Most experts believe combinations of drugs aimed at multiple targets is where the future lies. But testing unproven combinations on early stage patients is not the answer. Serendipity is not a strategy. Bergh asks: "If there is an effect or any side-effects, how

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are you going to tell which drug is responsible?"
Boyle is even less impressed. "I really don't think that rooting around in the bottom of the cytotoxic barrel, trying any combination we can get our hands on, is going to take us further forward. We did that in the 1980s. Since then we've been focusing on developing more effective and scientifically plausible approaches."
Cavalli agrees: "We simply do not understand enough about the molecular biology of these tumours to put together cocktails that can attack multiple targets. We need to improve our knowledge of the biology of the disease and that takes time."
Cavalli does blame regulatory authorities for some of the slow rate of progress – not because they are inflexible, but because they are too lax. "I think recently the regulators have made it too easy to get approval for drugs that are little better than what is already on the market. If you set the bar a bit higher, then you will oblige the pharmaceutical companies to develop research to come up with drugs that really make a difference."
Cavalli is not alone in wanting the drug companies to aim higher. Boyle suggests: "One way to deal with this could be to limit how many drugs of any one type can be on the market at any one time. In China, an extreme example, they only allow one drug in each class on the market."
All our experts cited the European Clinical Trials Directive as a brake on future progress. However, they point out that the directive is the work of the European Commission, and cannot be blamed on the regulatory agencies.

EUROPE'S RECIPE FOR SUCCESS

European experts agree that our ability to genetically profile individual tumours and analyse what is going on at a molecular level will eventually transform our ability to control, if not cure, cancer. But it will take time.
"Thirty years ago we did not know a single gene that mutated to cause cancer," says Barbacid. "We did not even know for sure – although we suspected it – that human cancer was caused by mutations in our genes. The first human oncogene was isolated in 1982. Now we have identified more than 260 different genes."
But the full story about how oncogenes mutate and how individual patients react still has to be unravelled. "…There must be some rules, but we still don't understand them," he says.
Bergh wants to see more early biopsies done in human cancers, including metastases, to develop our understanding of tumour progression. He would also prioritise finding ways of identifying patients who will respond to given therapies and ensuring drugs are administered in the correct dosage. Encouraging and investing in the next generation of cancer researchers – especially biometricians, bioanalysts and biostatisticians – is high on McVie's list of priorities. He also argues that we should be looking to the biotechnology sector rather than the risk-averse pharmaceutical industry for novel and imaginative approaches to drug development.
Moulon would like greater coordination between the work of research, industry and the regulators "so we can agree on where we want to go and how we want to do it." This is also highlighted by Kearney, who points to the newly established UK National Cancer Research Institute as a hopeful development.
Cavalli wants European governments to assume greater responsibility for funding research, rather than ceding the territory to the pharmaceutical industry. Drugs companies, he argues, start by thinking about the easiest way to get a drug approved for the largest market – the three or four most common cancers – and true collaboration is incompatible with their duties to their shareholders. "We have a wonderful structure of cooperative groups carrying out clinical studies in both rare and common cancers, but they have less and less money. Increasing support to these groups is one important way we could speed up our success."

MEDICAL ONCOLOGIST

Mario Dicato

Specialist and in Haematology and Oncology, Centre Hospitalier, Luxembourg

■ The surgeon is a prime factor for survival. If you have a surgeon without experience you will not recoup that by any kind of drug or other therapy.

■ It is certainly true that some drugs are more sexy and fashionable. After a number of years you realise it is essentially doing the same thing as the less fashionable, older, cheaper drug.

■ If you have a limited amount of money, my answer would be not to look for another fancy drug but to push early detection as much as possible.

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Some fear that the trend towards targeted drugs may lead pharmaceutical companies to abandon cancer markets as too fragmented and focus on diseases more susceptible to "blockbuster" profit earners. Iressa, after all, was trialled for lung cancer patients in general – it only later became apparent that it works only for a minority.

SCREENING AND EARLY DETECTION

Our experts estimate the time it will take to control most cancers at between 50 and 100 years. A number question whether in the mean time we should focus so many resources on the search for a cure, while neglecting other opportunities.

Most agree that there should be more emphasis on early detection – including detection of pre-carcinogenic lesions that are strong predictors of cancer. But there was a consensus that blanket screening is undesirable and unworkable. Kearney says "We need to be more focused. We should keep looking for biomarkers of certain tumour types and test those in small populations at high risk."

McVie echoes her point. "There is no evidence that blanket screening will be any better than an intelligent hypothesis driven approach to the same issues."

Bergh fears that a sudden change of approach could just be another way to spend money without results. "The cost of breast cancer screening is already contentious. We need to find a system that works not just in rich countries like the US, but over the whole world. We need to find methods that are rapid and cheap so you can screen large populations to find the very few who will benefit. More importantly, we need to stimulate research into how you cure lesions once you've found them."

Lynn Faulds Wood, a former patient and now a campaigner, believes that an effective screening strategy for colorectal cancer has been available for almost 30 years, but has been passed over. Flexible sigmoidoscopy, a short form of colonscopy, has dramatically increased the rate of early detection in California. It is cheap, takes five minutes, can be carried out by nurses, needs to be done only once or twice in a lifetime, and can pick up 60% of colorectal cancers, and most cancers in the rectum.

Prevention, too, could be given a higher priority. Boyle argues that if Europeans stopped smoking today, this would save 400,000–500,000 lives a year in 15 years time. Jassem, who works in Poland where money for patient care is particularly short, agrees. "We are trying to save lung cancer patients using very expensive medical therapy, whereas we can achieve far more by being more effective in primary prevention."

Kearney says "We've been paying lip service to prevention for the past 20 years across Europe. We have the Code Against Cancer and targets for reducing incidence. But if you look at things like smoking and diet and lifestyle, current health promotion strategies are just not working. The prospect of getting cancer in 30 years time is not an issue for young people."

Faulds Wood agrees. "We've got to be more creative at relating to youngsters who pride themselves in being reckless and bad, and don't think about their middle age." When she attended the first meeting of the UK policy advisory group on colorectal cancer, she was told that prevention was not part of their brief. "Every policy group dealing with cancer in every country should put prevention at the core of their being, and then work from there," she says.

QUALITY OF CARE

It was also pointed out that a great many lives could be saved by improving the quality of treatment using existing methods and knowledge. Jassem says "The majority of patients everywhere in the world are treated with local therapy, surgery or radiotherapy. Many will receive drugs as part of the treatment but this is not the main approach. If you take into account the proportion cured by radiotherapy and the proportion by drugs, the number of studies of radiotherapy is relatively low. These studies are not sponsored by the industry. They are mainly academic studies and face many difficulties not only due to poor financing but problems related to bureaucratic regulations."

He calls for better integration of the different approaches to cancer. "The final outcome consists of several aspects: prevention, early detection and treatment. We oncologists mainly deal with diagnosed patients and it is not easy to do all these things under one roof. But it should be a concerted action and this is what we are missing on a global scale."

There is growing evidence to show that the quality of surgery in cancer is critical to survival. Dicato cites a recent Dutch study on colorectal cancer showing the prime importance of surgical skill, especially in rectal cancer, and adds: "The surgeon is just as much a prime actor in cancer of the breast and the lung because if you don't get to a surgeon there is no hope whatsoever. If you have lung cancer that is inoperable then you start counting in months and maybe the drugs give you a few more weeks."

Dicato would give a stronger push to prevention and early detection,

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"rather than wait for advanced disease and then come in with complicated and expensive drugs." But every day in his hospital he sees why this cannot be the only strategy. "The reality is that the stream of patients is endless who need chemotherapy because they have advanced cancer and they come at a point where we are beyond screening. Even if I am convinced it would be better to prevent advanced disease and see them earlier on, I still have all these patients every day who don't fit that category."

Kyriakides says that since we do not know how to prevent breast cancer, we have to focus on early detection and treatment. "The European Union statistics say that we have a new diagnosis every 2.5 minutes and every 7 minutes a woman loses her life. Our primary goal is to fight the battle against breast cancer not just in terms of finding a cure, but also to improve the life conditions of women and the few men living with the disease.

"We are advocating for national screening programmes which adhere to the European screening guidelines, and for breast cancer to be treated in centres of excellence as breast units which are accredited and meet the European guidelines for treatment. Then women have the best chances of good long term survival, and in many cases cure, when it is detected very early."

Apolone would make his priority better trained doctors and better facilities. "Of course it is important to have good research. It is also important to have money to take care of the disease in all the patients in all the cities and villages of Italy. It is assumed that the translation of knowledge into practice is automatic, but that is not true. You have to allocate the money for education and also facilities in order to be able to give the best care to everyone. We have to split up the money between research and practice. There is a sort of competition to do that. You could improve the management of cancer patients in a short time; three, four or five years."

For people with advanced cancer there is a difficult choice to be made. Are the few extra months of life offered by many cancer drugs worth the possible damage to their quality of life? And, (even more difficult) would the money be more effectively spent on better palliative care for themselves and other cancer patients?

"If there is a recognition that people are living with cancer, then we will have to pay more attention not just to finding treatments for cure, but how to allow people the best quality of life with supportive care. We need that dialogue," says Kearney.

Faulds Wood, who is Chairman of the European Cancer Patient Coalition, agrees. "My son was three years old when I was diagnosed. The fear that you are going to die, leaving that child without a mother or a father, is incredibly strong, and you would deal with the devil to survive. But we need to be more honest with patients about how much extra time they may get, what it costs the country and what it costs them in terms of the way they feel. I don't think that honesty is there at the moment.

"Give us genuine information about the likely benefits, and the costs to the health service and to your quality of life.

"I would like to see patients getting together to listen to expert opinions and thrash this issue out."

Apolone too believes that choices have to be made. "If you spend too much money on this kind of drug you do not have the money to increase the number of good physicians able to give the best treatment to patients. The problem is not just physicians but also public opinion and the families. If we send out the message that the only solution is to have a major new drug, people ask for the drugs. We have to educate people that there is no magic way to cure such a complex disease, and most of the time new drugs are no better than the old ones."

Maybe this sounds like surrender, or maybe it is shifting the battle ground, or maybe it was never a war in the first place.

"This whole idea of losing or winning a war is a very American one," says Cavalli. "This was the big mistake that was made when President Nixon declared that in 20 years we will have conquered cancers like we were able to conquer the moon. Winning the war would mean that we know almost everything about the most hidden secrets of how life functions – nature would hold almost no more secrets from us. In reality, results are improving very slowly and at different speeds in different cancers. It will take 60 to 100 years till we can cure all cancers – it takes physiological time. Anyone who thinks we can win in it in five years doesn't understand the problem."

Kearney agrees: "We have to stop talking about this as a war that you win or lose, and we have got to get away from this concept that we can cure everybody with cancer, because it's not that kind of disease. Most of the resource has gone into winning the battle to find a cure, rather than prevention, supportive care, the process of the illness and how to manage it. We need to focus less on the cancer and think more about the people who have it."