A simple doctor's quest to improve on today's treatments

How Stan Kaye came to lead drug development at the Royal Marsden

➜ Simon Crompton

Treating patients who are urgently searching for new therapies is tough and doesn't get any easier, says **Stan Kaye**, head of drug development at the Royal Marsden. He treasures the moments when a new drug turns up that shows real value. The big challenge for medical oncology is to understand who benefits from what; success depends on attracting to the field the brightest and the best.

By his own assessment, he is a "simple doctor", not a scientist. Stan Kaye works in an office of few pretensions, displaying pictures of past players from his beloved Leeds United Football Club rather than professional accolades. He is quiet but avuncular, and says he was never particularly ambitious. Yet it was a simple doctor's motivation – to end the suffering brought on patients by frankly inadequate cancer treatments – that brought him to lead one of the most important early clinical trials units in Europe.

As head of the Drug Development Unit at the Royal Marsden Hospital in Sutton, England, and the chairman of the Institute of Cancer Research's Section of Medicine, Kaye is now overseeing the first use in humans of a range of new targeted therapies that could transform cancer treatment in the next decade.

He finds it hard to conceal his excitement, for instance, about the potential of PARP inhibitors – a class of drug whose possibilities were first recognised by scientists at the Institute of Cancer Research six years ago, and were subject to their first extended single-agent clinical trials at the Royal Marsden three years ago. The drugs have yet to reach the market, but there is accumulating evidence that they will bring significant benefits to many patients with breast and ovarian cancer, and possibly others including prostate, endometrial and colon cancer.

"We are genuinely moving from chemotherapy to much smarter treatments based on a better understanding of what causes cancer, and what distinguishes cancer cells from normal cells," he says. "This knowledge is being turned into new treatments, often given as tablets, that make people's tumours shrink, and it's just terrific. So in the next few years there's going to be an increasing understanding that you don't treat all people with a particular type of cancer in the same way, and indi-

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vidualised treatment will increasingly take over."

It's all a far cry from his early days as a researcher in the 1980s, when he was driven by seeing how "lousy" current treatments were. The past five years is bringing something truly different, and he can afford to be optimistic.

Kaye's excitement about PARP inhibitors is related to his own special interest, ovarian cancer, where the drug is showing particular promise in helping both common types and rarer familial forms linked to BRCA mutation. During phase I trials at the Drug Development Unit, Kaye and his team on the clinical side worked closely with scientists who had developed the drug. In the first trial, 19 patients with advanced ovarian, breast and prostate cancer, who were all BRCA gene mutation carriers, were given the new medication, having exhausted other forms of treatment.

"Early on, even in the first patients treated, we knew we were on to something. It only happens rarely that you see a new treatment really making a difference at this early stage. We couldn't believe the first data because, in half the patients, the tumours shrank. The drug had very modest toxicity and patients said, 'This is nothing like chemotherapy.' So we were delighted when an international trial showed the same thing – roughly 50% response rate in recurrent ovarian cancer." The drug could constitute a significant leap forward for ovarian cancer, Kaye reflects, where developments have been slow in recent decades and largely focused on improved multidisciplinary care rather than good drugs.

The Drug Development Unit at the Royal Marsden, one of the biggest in the world, is buried in the hospital's sprawling site in Sutton – Lego-style blocks, puddle-strewn car parks, a muddy building site and the faded Victorian monument where Kaye has his office. Around 600 patients with cancer that

WHO BENEFITS FROM PARP INHIBITORS?

Mutation of BRCA1 and BRCA2 genes has been linked to hereditary breast, ovarian and prostate cancer. In 2005, the Institute of Cancer Research team in Chelsea, led by Alan Ashworth, discovered that, because these genes were not functioning, DNA repair was defective, and these cancers were therefore exquisitely sensitive to drugs blocking an enzyme called PARP. Early trials of these PARP-inhibitors at the Drug Development Unit showed that around 50% of tumours shrank. This result was replicated in an international trial. Last year, it was announced that Ashworth's team had discovered that the drug would also kill cancer cells with other types of gene faults apart from BRCA inherited cancers, so its potential is much broader than originally thought. The drug is now moving into phase III trials. According to Kaye, the beauty of PARP inhibitors is that doctors should be able to predict exactly who will benefit from them, because the genetic defect that makes people responsive will have a biomarker.

has progressed despite conventional treatment come here every year to enter phase I trials of experimental cancer drugs, knowing that the odds are that the drug won't help, but that there is a chance that others will benefit from the knowledge gained, even if they do not. The centre takes the genetic discoveries made at the Institute of Cancer Research's facilities in Chelsea, London, converts them into drugs, and offers them to patients with advanced cancer. Funding comes partly from the drug companies that are jointly developing the drugs, as well as from Cancer Research UK and the Department of Health.

TRANSLATING GOOD SCIENCE INTO GOOD TREATMENTS

In the 10 years that Kaye has been in charge of the centre, he's closed the gap between the hospital and the Institute of Cancer Research, distilling a disparate phase I operation scattered across the hospital into a single specialist ward with 25 nurses, 15 doctors and 80 staff all working exclusively on the trials. These changes involved major restructuring at the Royal Marsden Hospital site at Sutton.

It produced a centre that is leading the way, not only in drug development, but in the way that early trials are performed. Phase I trials, believes Kaye, are about to become more important than they have ever been, and the Royal Marsden's dedication to speeding up the translation of good science into good treatments is showing the way ahead.

Towards better treatments. Catching up with fellow specialists at the 4th Ovarian Consensus Conference in Germany, 2004

"The nature of phase I trials has changed a lot since we conducted our first one in the mid-1980s in Glasgow. For instance, I did a trial with a drug company of a green compound. It had some striking effects in the experimental model, and it seemed safe enough, but it went into the clinic without me having any idea of how it worked. This is something we would rarely do now. We need to know if a drug is hitting its target, and the way they are assessed involves sophisticated biomarker work. You just wouldn't do trials now without all that, but in the old days we did."

"It will continue to get better if we get smarter at finding out which patients should get these targeted drugs"

"Oncology requires no specialist manual skills, so it stands or falls on the quality of people who come into it"

The result is likely to be safer treatments and a more rational basis on which to decide whether or not a drug might go forward. The majority of drugs fail – less than 10% of the drugs that go into phase I trials succeed. "But its getting better," says Kaye. "It will only continue to get better if we get smarter at this whole business of understanding which are the patients who should get these targeted drugs."

Nowadays, phase I studies are far more than the experiments in safety they used to be. "They aim to establish correct dosages, indicate substantial activity, and to expand the number of patients involved with a real expectation of benefit."

Kaye continually emphasises that patients need to be realistic about the prospect of significant improvements in phase I trials. But the chance of benefit is still there; for instance, in a study published in 2010, potential clinical benefit was seen in up to 20% of women with metastatic breast cancer taking part in trials of novel approaches at the Marsden between 2002 and 2009 (*Br J Cancer* 103:607–612).

Though phase I trials for cancer drugs inevitably involve only those with advanced cancer who have exhausted all other options, the findings from these trials often have implications for treating cancer at much earlier stages. So for individual patients, and the greater cause of developing better cancer drugs quicker, Kaye believes that an expansion of phase I studies – not just at the Marsden but nationally and internationally – is the way forward.

"First-in-man studies are very demanding. You are having to give small numbers of patients escalating doses, and work out over the course of six months or so what might be an appropriate dose and what the ups and downs of that drug could be. Having got to that point, you need to understand whether that drug is going to be successful – and you may well want to treat a number of patients with a particular tumour type or particular molecular characteristics to understand more. For that kind of work, where you've gone beyond the first-in-man part, we need more facilities. Cancer Research UK is setting up networks across the UK to help with that process."

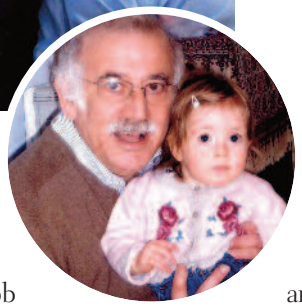
"So the distinction between phase I and phase II studies is blurring to such an extent that conventional phase II studies may not in some cases be appropriate. Having established a significant level of activity in an expanded phase I study, the next step might be a randomised phase II study." The days of single-arm non-randomised phase II trials may be numbered, he says.

An accidental oncologist

Kaye is what you might call an accidental oncologist. Born and bred in Leeds, his father was a Polish leatherworker (his name was originally Krakowski) who came to Britain with the Polish army during the last war.

Kaye ended up going to medical school because he was good at biology and chemistry at school, and his parents wanted him to follow a profession. Those he studied with at Charing Cross Hospital have

Vital support. Meg Morrison, of the UK Cancer Research Campaign (forerunner of CRUK) presents a cheque, dated June 1988, to support the research work being carried out by Kaye and his colleagues at the University of Glasgow



Three generations. With his wife Anna at their daughter Sarah's wedding, and (right) with his first grandchild Hollie, December 2010

remained lifelong friends. One, Bob Leonard, a football and squash pal, had started a job in oncology at Charing Cross Hospital and urged Kaye to join him, a year after qualification. Kaye knew little of oncology, but was looking for an interesting hospital job at that time.

He came under the supervision of Ken Bagshawe, one of the founding fathers of medical oncology in the UK, and was bowled over by the lifesaving potential of chemotherapy for young women with gestational trophoblastic tumours, who came from all over the country to be treated by Bagshawe and his team. "Their recovery was remarkable, and I thought: this is great. I knew I wanted to be an oncologist."

The experience has been influential throughout his career. Oncology, he points out, is a new specialty, which has changed immensely over its 40 years. Unlike specialties like surgery, oncology requires no specialist manual skills. "That means it stands or falls on the quality of people who come into it," says Kaye. He believes that inspiring others to follow is part and parcel of what oncologists should do, and like Bagshawe he has tried to open other doctors' eyes to the potential of the specialty.

He was able to do this during 20 happy years in Glasgow, where he took up the post of senior lecturer at the University's Department of Clinical Oncology in 1981, becoming professor and head of the Medical Oncology Department in 1985. It was a small unit, which grew substantially over 15 years, and Kaye was busy covering a wide range of clinical areas. The students and doctors he taught there have become part of a "Glasgow mafia" that he has maintained contact with. One is Johann de Bono, who joined Kaye at the Institute of Cancer Research eight years ago, and uncovered the exciting potential of the new hormonal therapy abiraterone to treat cases of advanced prostate cancer.

"There are people here who may prove to be more successful than me. One of the things I enjoy most is encouraging and watching young folk who are involved in this area, and because of the reputation of the Drug Development Unit, we get super doctors from all over the world."

Kaye's clubbability has served him and those he has inspired well, and it's a matter of satisfaction to him to see what such informal networks achieved. He became involved in the European Organisation for Research and Treatment of Cancer in 1980, chairing the Early Clinical Trials Group and the Scientific Audit Committee. "Drug development then was a completely different world. We worked in a small group of just 12 or so European colleagues," says Kaye. Drug companies didn't seem so committed to drug development in cancer. "What's changed is there's been so much expansion, so much to work with, so much to learn, that we've lost the concept of a relatively small group of people working together, and EORTC doesn't need an Early Clinical Trials Group because all the major centres are doing their own thing." While that is a welcome development in some ways, Kaye emphasises that maintaining links across Europe between like-minded clinical researchers remains essential.

Driven by the tough end of cancer

Kaye's stories of drug development often incorporate tales of patients' faces lighting up, or their generous comments. His relationship with them – whether it be inspiring or problematic – has always been foremost in his motivations. "My research was always from the point of view of someone whose main job was seeing patients with cancer. If I have any kind of mission, it's that I've been seeing the tough end

ROYAL MARSDEN HOSPITAL

Meet the team. All phase I trials at the Royal Marsden are carried out in a single specialist ward by this dedicated team of medical, nursing and support staff and research fellows

of cancer treatment for a long time, and I don't like it really. It's tough. It doesn't get easier looking after young patients who are desperately looking for new treatments because their disease is going to be fatal. I think that links together with my sense of what the new science offers, to drive me."

He's now 62 and revelling in the recent birth of his first granddaughter. His wife and eldest son are both GPs, and he has two other grown up children who have flown the nest (one a teacher and one an embryo film maker). Though he admits to wanting – one day – to see a bit more of the world than he manages to glimpse from airports and international conference centres, he's not banking on retiring just yet. There are too many plans to put in place.

Out of those muddy puddles between the Royal Marsden buildings is about to spring a new Centre for Molecular Pathology – a research centre, funded through Department of Health research support, that will speed up the process of introducing personalised medicine in daily patient care. It links with Cancer Research UK's initiative to introduce "stratified medicine", where patients with cancer have their tissue sampled with state of the art molecular techniques, to diagnose and target treatment. This is already part of what the Drug Development Unit does, but now, with the new Centre, there's the potential to make their pioneering techniques more widely available to cancer patients. And ending "lousy" cancer treatments for good.

"What's most exciting now is the potential for targeted treatment on a routine basis – patients having their tumour DNA sequence recorded regularly," says Kaye. "It needs expensive equipment, and the Centre for Molecular Pathology will help us with that hardware. I'm hoping that, over the next few years, that will become a standard procedure here, and if we can show the way, I think it's feasible that it will become available nationally."

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