Jean-Yves Blay

integrating translational and clinical research

Marc Beishon

Major clinical breakthroughs come from understanding molecular biology. So says EORTC president Jean-Yves Blay, who is leading efforts to reshape cancer research so that every trial has a translational element that can build knowledge about the mechanisms driving the disease.

If the fight against cancer is mainly an incremental process scientifically, building carefully on evidence, step by step, the same approach should apply to the people and agencies working on the problems. This means that, in the clinic and in research, we need to keep refreshing the centres and team leaders, and generate a continuous stream of young investigators, to ensure that the brightest and the best are in a position to help move things forward. Without this, momentum can slow down or even stop.

That is the firm view of Jean-Yves Blay, the current president of the European Organisation for the Research and Treatment of Cancer (EORTC), who can himself be seen as an injection of new thinking at the head of an organisation that is at the forefront of many critical issues in oncology. Heading the EORTC is one of the most challenging jobs in European cancer, as there are so many obstacles in the way of unifying research efforts around the continent – not least the differences in national healthcare systems and in the rules and regulations governing research, the lack of resources and, in recent years, the huge impact the Clinical Trials Directive is having on academic studies and groups. And the EORTC has faced criticism – notably that an 'old guard' has been in place for years.

"The challenges are certainly real and the criticism we've had is fair to some extent," says Blay, adding that the problem has been greater in some parts of the organisation than others. "We are made up of a number of research groups, and some are very active, although others have gone through a lifecycle where we need to bring in new blood. The EORTC board, with director Françoise Meunier and Denis Lacombe from the headquarters, has asked each group to identify young investigators and we are holding meetings to help them become involved, and we have closed some groups while others are starting again from scratch."

The EORTC is also looking much more towards collaborating with other networks and agencies in intergroup studies to avoid duplicating efforts and get the most out of limited resources. "What is

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clear though is that the EORTC is probably the only body with the long-term expertise to organise clinical research in a range of cancers across countries in Europe," says Blay, "and we have other groups coming to us for this experience and not just to add patients to their studies."

Another part of the EORTC's strategy is to focus on a smaller number of expert centres to carry out complex and demanding clinical and translational trial work. The Network of Core Institutions (NOCI), under discussion for many years, has now been set up for this purpose. Last year agreements were signed with core centres – there are 26 now. They will implement complex molecular trials, but will, says Blay, also involve smaller centres, when needed, via EORTC's disease-specific groups. But smaller centres do lack the patient numbers and multidisciplinary groups needed to participate in increasingly complex translational research studies.

"The door is always open, but we must have centres capable of contributing a high level of accrual in studies, expertise in rare tumour subtypes, excellent molecular biology facilities and so on – and even the top centres do not have all the resources and people on their own. There are hundreds of new, targeted agents in development and hundreds of tumour subtypes, with more being uncovered each year. We simply do not have the resources to test

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combinations in an empirical way anymore and we must truly integrate translational research for rational treatment development that is both effective and less costly to carry out."

Blay's main job is professor of medical oncology at the University of Lyon and head of the medical oncology department at Lyon's Centre Léon Bérard, one of France's top dedicated cancer hospitals. As befits someone entrenched in the intricacies of translational research, he is a rare tumour specialist, having opted to focus on sarcoma from an early stage of his career.

That means he has been closely involved with the development of treatment with the standout targeted drug Glivec (imatinib) in the treatment of gastrointestinal stromal tumour (GIST). But as a medical oncologist who attends virtually every major cancer research conference, he is also familiar with most of the promising new drugs and their molecular targets, not least because some are in EORTC trials.

"We are now seeing several examples each year of new targeted agents, such as that targeting ALK, with effect in both a rare tumour and a subtype of common tumours such as lung cancer. Another example is an agent targeting RANKL that exerts Glivec-like tumour control in a rare cancer – giant cell bone tumour – it has about 95% control, but also potent antitumour effect in bone metastases of more common tumours. We are also seeing a success story with the RAF inhibitor for melanoma developed by Plexxikon and now Roche. Crizotinib, an ALK inhibitor, is being evaluated in lymphoma, sarcoma and other rare tumour subtypes in a NOCI trial in the EORTC. It is this kind of translational research – where we select subtypes of patients with different, non-standard diagnostic tests – that we are setting our sights on now, in what should be practice-changing trials."

Most medical oncologists with strong research interests have of course focused on biological target selection for some time, but as Blay adds, actually pulling together the resources to get speedy answers

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"It is harder for a team to keep in touch with patients on oral therapies and address their concerns"

to the right translational research questions is still a huge challenge. Having the right sort of platform in NOCI, together with other partners in Europe and further afield, is at least an important step forward he feels. His own contribution to French translational cancer research – he has helped put the country on the international map – and his confidence and infectious enthusiasm no doubt played a role in the decision to elect him to the EORTC presidency in 2009.

Blay comes from a family of doctors – including both parents and various other relations – and he says he was 'predisposed' to go the same way. "I did my medical training in Lyon and had my first placement at Léon Bérard, and from then on I didn't want to do anything other than oncology – I wanted to work in a difficult area with great promise for development and I wanted to do research."

He then spent a year at France's top cancer centre, Gustave-Roussy in Paris, training in research, where he was fortunate to come under the wing of the renowned and late medical oncologist Michel Clavel, who encouraged him to look around for research topics – and also to become involved with the EORTC. "I did my PhD on immunotherapy in cancer, but also looked at tumours that were not already crowded with researchers – and some then were almost 'unknown lands', including sarcoma. We could see that what we were learning about molecular biology would one day translate into treatment, but it did take some time."

Blay was offered an assistant professor's position at Léon Bérard and proceeded to develop a research-based clinical career during the 1990s, working on a range of cancers, but primarily sarcoma, lymphoma and kidney, trialling high-dose chemotherapy, continuing his work on immunotherapy with agents such as interleukin, and heading a cytokine ('immuno-modulating') research lab that is now part of a major cancer research centre. Léon Bérard, he says, is now second in clinical research in France after Gustave-Roussy, and in and around the centre are an increasing number of labs and partner agencies.

Sarcoma did indeed become fertile ground for Blay, but the first major breakthrough from the medical oncology standpoint did not come until the identification of GIST as a distinct molecular entity, and soon afterwards the introduction of imatinib, which fundamentally changed treatment for this type of sarcoma. "Then in about 2002 we came to the understanding that other sarcoma subtypes needed different treatments based on molecular typing and surgical classification, and that is what is driving research into new agents now – understanding the molecular biology and designing rational treatments that target the tumour's causation event."

As Blay points out, molecular differentiation has now uncovered as many as one hundred sarcoma subtypes, and he expects at least another hundred more. "For example, we've found some very rare molecular subtypes such as a Ewing sarcoma where there may only be about 15 cases a year in Europe, while in the more common liposarcoma there are three completely different molecular subtypes that need different treatment."

Actually treating patients is also changing, as new agents, particularly those taken orally, are reaching clinics. "We used to do mainly in-patient clinics where people would come for two to three days of high-dose chemotherapy. Now we have mostly outpatient clinics, as 30% of people are taking only oral drugs and some IV chemotherapy can be done in an hour or so," says Blay. But this does bring other pressures. It is harder for a team to keep in touch with patients and address their concerns, and in France, as in some other countries, reimbursement for giving oral drugs is much lower than for administering IV-based therapy, which he says could raise funding problems in the future.

France had been lagging behind some other countries in the management of sarcoma patients, notably the UK and Scandinavian countries, says Blay, but he adds that the French sarcoma group, which he co-chairs, has started to follow by agreeing funding for

a concerted national referral programme to major centres. "This started in 2009 and is progressing well. It is also mandatory under our national cancer plan for all patients to have a multidisciplinary assessment, although we are still far from this target. One problem is manpower – if you aim to have a large team of specialists discussing all cases, it may be that some of their time is better spent somewhere else. But we have shown in a small local study in Lyon that patients who do reach a multidisciplinary board may have a better progression-free survival – about 20%." About 10% of French sarcoma patients are now in trials, he adds, although in the UK, one of the European leaders, it stands at about 18%.

Now, he adds, a much larger study is underway comparing the management of sarcomas in the Rhône-Alpes region with national recommendations and with other regions in both France and Italy, again to demonstrate the impact on survival. This work is led by a certain member of his group at Léon Bérard, namely Isabelle Ray-Coquard, a medical oncologist who also happens to be married to Blay, in what must be one of the closest personal/professional partnerships in European oncology.

SIMON BACONNIER

Partners. With a group of patient advocates at the first Conticanet Patient Advisory Group workshop, Paris, 2006

That study is work that was part of Conticanet, a 'network of excellence' for connective tissue tumours funded by the European Union's sixth framework programme (FP6), and which has now ended. Blay was the coordinator of the project, which aimed to improve the molecular characterisation, management and treatment of what many think is a rare disease group, but which does affect up to 10,000 people a year in Europe. As usual with these projects, which comprise a number of work packages, Blay says what was actually achieved was different to some initial proposed outcomes: "But I suspect something is not going well if it's not changing or evolving," he says. Two particular changes he mentions are including molecular subtypes in cataloguing the epidemiology of sarcomas in Europe, and integrating academic research on surgical and radiotherapy treatment, and also imaging. Blay helped set up a Europe-wide patient group as part of the project, the Sarcoma Patients EuroNet Association (SPAEN).

These framework programme projects have the aim of leaving a sustainable legacy, and one Blay is particularly pleased about is a virtual tumour bank, which so far has 10,000 paraffin and fresh-frozen sarcoma samples (see also Cutting Edge, p22). "This is accessible by anyone in the world, with agreement for research based on each contributor, and should be a good model for rare cancers – anyone can contribute provided they meet quality guidelines such as central pathology review, and we will see if it will be used to identify new treatment targets."

Even without Conticanet, Blay says that the world of sarcoma researchers has been particularly close and there is a good deal of cooperation on who does what work. Researchers from some countries, China, for example, have recently joined clinical trials for the first time, and he says multinational collaborations are increasing rapidly. And clearly, as the complexity of translational research increases, the issue of how centres cooperate to answer the right question in any cancer type will be crucial.

"I have done a lot of translational research, and much of it has been what we call descriptive, or

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more harshly, cosmetic, where we may not understand the mechanisms, and of course we must carry on supporting this work. But now we need much more to build what I call integrated translational research, which is our aim at the EORTC and was set in train by my predecessors as president, Martine Piccart and Lex Eggermont."

Taking his own work to explain the progression in translational research, Blay says one of his most cited earlier papers found that patients responding to immunotherapy with IL-2 (interleukin-2) did less well if they were overexpressing a factor called IL-6 during treatment. "This is probably true and has been reproduced by others, but it did not go much further. But another study looked at a serum test to identify patients who would not benefit from treatment and we were quite successful in also correlating VEGF level with a lack of response. This was confirmed later by other studies, not just those on immunotherapy, and is an important phenomenon that may have contributed to the development of VEGF inhibitors in kidney cancer, in particular in combination with interferon.

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"Then we had another example, the EORTC phase II trial of imatinib in GIST, where in one arm we showed there was 90% control in GIST and none in non-GIST sarcoma. That was proof that selecting patients on the basis of a molecular alteration made sense. And finally an example of truly integrated translational research was finding that GISTs with a certain uncommon mutation (PDGFRA) were not going to respond to imatinib, so we can now identify these patients and drive them to another protocol where there is response."

A recent example that has been a major translational research success for the EORTC is in glioblastoma (a high-grade brain tumour), where the drug temozolomide was found to benefit mainly patients with an inactivated repair gene called MGMT.

The most well-known translational study coordinated by the EORTC is, of course, MINDACT, large-scale research using gene expression captured on microarrays to improve the selection of breast cancer patients who can be spared chemotherapy. "I know there are strong opinions about it, and I accept that some see MINDACT as a complex academic exercise, but it is important not only because of the question but also for demonstrating that such research is feasible at this level," says Blay. "If it shows improvement in patient survival, that will be a real proof of the clinical value of the gene expression concept, and if not, then we will go in another direction."

He is still sceptical though of the applicability of gene expression in routine practice, although he does not doubt its value. "It offers an integrated view of genes being expressed in the cancer cell, but it may be hard to apply ultimately in clinics outside of major centres. What may be reproducible are the

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structural alterations of DNA – there are easier tools to test things like amplifications from paraffin embedded tissue."

So one direction for research is the smaller trial on more focused populations of defined molecular subtypes, where the value of large-scale randomised trials can be less useful, says Blay, pointing to the ten or so key targets now in play, such as RAF and ALK. "If the population is not homogeneous enough, of course we will be doing large randomised controlled trials, but we may not need them for certain agents with a targeted population when an outstanding clinical benefit is observed, imatinib being a prime example."

A thread common to both types of trial is increasing organisational complexity, given the need to link a wide pool of researchers working in different countries and continents, often across different cooperative networks, to accrue both expertise and patients, especially for rare subtypes. As Blay points out, there are two main types of clinical trial – drug development, where there is usually industry input, and therapeutic strategies, which really need multidisciplinary approaches, and for which funding is hard to find for independent academic research.

Although much early-phase drug development is done in the US, Blay talks of seeing encouraging signs that industry is investing in European centres, thanks to the quality of the researchers, "and possibly we are better placed for the focus on accruing patients for subtypes – a well understood molecular pathway is a good way to get to market now." And while major obstacles still stand in the way of academic research, the EORTC has found ways to mitigate the worst effects of the Clinical Trials Directive, which reduced the number of EORTC trials to a mere handful when it first came into force. The Directive is now up for revision.

Blay is keen to stress that the EORTC will be networking more widely on research, and will be happy for agencies such as the UK's Medical Research Council to take a lead on projects, for example, while the NOCI grouping, he says, will be a "truly efficient network instigating new trials that have molecular alteration as an inclusion criterion." NOCI is, though, currently dominated by centres in northern Europe and especially France, the UK and the Netherlands, and Blay acknowledges that there is still too much fragmentation in research networks around Europe. The EORTC itself has a budget of less than €20 million – a far cry from its main international partner, the National Cancer Institute in the US.

Nevertheless, the EORTC, which is funded mainly by charity, is probably the most successful, long-standing cancer research network on the continent – and Blay intends it to stay that way. "It is critical we involve more young investigators so that EORTC research groups do not lose momentum – and it's a great way to develop a career as they will become better known to colleagues in their own countries." The quality of younger researchers who do get involved at European level is good, but it is a self-selected group – "It is a challenge for oncologists to keep up with the latest in molecular biology."

Another area of fragmentation that concerns Blay is what he terms the 'double culture' of basic and clinical scientists when it comes to translational research. Unusually for a clinician, perhaps, he would like to see more invested on the basic side, while maintaining clinical levels. "Major clinical breakthroughs come from understanding molecular biology, but we have to bring the two groups together more." Biologists need to understand that, while they have complete control of experiments in their labs, they have to adapt to reality in the clinic, where say collection of specimens is subject to what surgeons and pathologists can provide, and ethical and legal constraints. Networking meetings for clinical and basic researchers are now key events in Lyon, he says.

Like many senior oncologists, Blay's own research interests have expanded rapidly during

his later years and he is probably one of Europe's most published lead and co-authors, with more than 300 papers, principally on sarcomas, GIST and immunotherapy, but also on public health issues such as breast and prostate cancer screening programmes. A quick glance at his CV though can miss the fact that in 1999 he moved from the cancer centre to head the oncology unit at the nearby Edouard Herriot university hospital, where in a nine-year spell he experienced being just another specialist competing for attention.

"When I arrived, some welcomed me but others said things like, 'I'm an organ specialist doing research on cancer – I don't need an oncologist' – and it was very challenging to convince people to work together as we built up an in-patient department for chemotherapy there. I had the higher mission though of merging its cancer activities and that of other hospitals in Lyon with Léon Bérard, and we have been quite successful, particularly in rare tumours. We now bring together physicians from different sites into a sarcoma board so we can allocate patients according to the best surgical specialists, for example." However, in countries where reimbursement is based on activity, and money can disappear when referrals to other hospitals are made, there can be major obstacles to setting up this type of treatment networking, notes Blay.

Since 2009, Blay has been back at Léon Bérard, and has the flexibility to devote at least a day a week to his EORTC work, along with clinical and research activities. He is studying very rare sarcomas, while his immunotherapy research has moved on to reconstituting the immune system rather than attacking the tumour itself. "It's completely different from the immunotherapy work of the 1990s," he says. The work has included showing that breast cancer cells 'subvert' the immune system to their own advantage.

He has long been a human dynamo, constantly on the move – colleagues speak of phenomenal drive and unlimited energy, despite him seemingly never eating lunch, which is very unusual in France. He is said to be a superb diplomat in the 'oncopolitics' of the European research community, taking on many organisational tasks with charm and tact (and never saying 'no'). Combined with his leading position in clinical and translational research, this makes him a key player across several fronts.

Close international colleagues include Paolo Casali in Milan and Allan van Oosterom in Belgium (both sarcoma experts) and Jaap Verweij, a top medical oncologist in Rotterdam. In France, mentors have included Clavel, and two now retired key cancer centre directors, Thierry Philip at Léon Bérard and Thomas Turz at Gustave-Roussy.

As if being in perpetual motion on the cancer front was not enough, Blay has a family of four children and finds time to also listen to a huge music collection and sometimes go snowboarding.

Will cancer research have a downhill run to success? Blay is certainly intent on moving things on as fast as possible. "I want to see true personalised treatment in selected groups in routine use in five years' time – that way we will really improve survival – and I want to see the EORTC and others doing more of the high-quality translational research we need to do this."

PIERRE HEUDEL

A close partnership. Blay's wife, Isabelle Ray-Coquard, chairs the gynaecological clinical research group of INCA, the French cancer research body, but she also shares Blay's interest in sarcoma and GIST