Lost in translation

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Cancer drugs often deliver less than they promise. The BDA believes the problem may lie not in the drugs themselves, but in the way they are targeted, tested and used. It organises regular get-togethers where the main players can share information and discuss strategies for the future.

With all the amazing imaging technologies now available, we should be able to design drugs to intervene with surgical precision in patient populations identified by predictive biomarkers. So why is it that most of the targeted drugs that have made it to the market have been less than spectacular successes?

Is it that cancer cells are too devious – they will always be one step ahead, finding little known back ways or creating new ones when their main pathways are blocked? Or is it simply that drug developers are having trouble getting their science right?

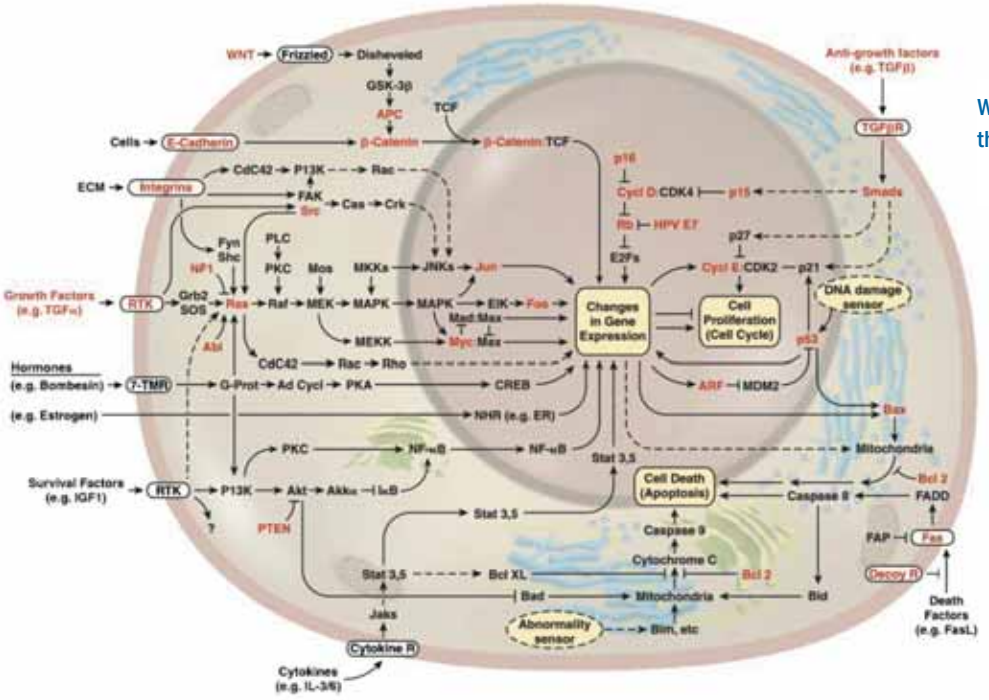
Heinz Zwierzina, chairman of the Biotherapy Development Association (BDA), is convinced it is the latter. He cofounded the Association in 2002 in order to promote the effective development of the new generation of cancer biotherapies. Zwierzina believes effective new therapies are being discarded at an early stage of development because of failings in the translational research and trial protocols. By the same token, he argues that many drugs that have made it to the market could be used to far greater effect if further work were done to establish the most effective dose and schedules, and to define the most responsive patient group and the most appropriate treatment setting.

One answer lies in bringing together drug developers, clinical research organisations and companies involved in diagnostics with regulators, translational and clinical researchers, and patient organisations, to try to develop a common approach to getting effective drugs to market. To that end, the BDA organises select conferences every 18 months, where representatives from all these areas meet in a secluded atmosphere, mull over the implications of recent developments and talk about lessons for the future.

Uncharted territory

The second such conference took place in Innsbruck at the beginning of October, under the title "Harmonisation of next-generation oncology drug development".

The need for harmonisation has come about because new imaging techniques have effectively torn up the traditional drug development rule book. Not only is this uncharted territory, there is not even agreement on how to conduct the exploration. Which of the burgeoning alternative tests and technologies are most appropriate for measuring what? Which biomarkers have a real clinical relevance and what do they tell us?



We are only just beginning to map the complexity of cell signalling pathways

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Which protocols are most appropriate for drawing out the information we need to use a drug to maximum effect? These conferences aim to establish and expand common ground. And some common ground there certainly is.

For instance, it is commonly accepted that targeted drugs are generally very much less harmful than cytotoxics, which means less need for phase I trials – many trials are now collapsing the phase I into a single phase I/II.

Phase II trials, however, are now seen as absolutely essential. No longer are they just pilot studies to see whether it is worth investing in a phase III. They should be exploratory trials using translational research to try to establish proof of the principle of the mechanism of the drug in humans, to identify the characteristics that predict which patients will respond best, and to establish the most effective dose and schedule. Well that's the theory anyway.

Nick Botwood from AstraZeneca talked about the lessons they had learned from the development of Iressa (gefitinib) – a drug for non-small-cell lung cancer (NSCLC) that AstraZeneca withdrew from review by the European Medicines Agency (EMEA) very early in 2005 because some impressive evidence of tumour regression in early clinical trials did not translate into a statistically significant increase in survival compared to placebo in the overall population.

Iressa had been designed to work in patients with NSCLC exhibiting EGFR over-expression identified using an immuno-histochemistry test.

However, it has since transpired that there are at least four communicating receptors, some more important than others, and 14 possible mutations have been identified, each associated with different levels of response. It now turns out that Iressa actually works best in patients exhibiting an amplified EGFR which does not show up using immuno-histochemistry, but is detectable by the FISH (fluorescence in situ hybridisation) test. However, in the meantime, Roche got approval for a rival drug, Tarceva (erlotinib), whose phase III

IMPACT OF VEGFR-2 INHIBITORS ON OTHER TYROSINE KINASES

Compound	Phase	VEGFR-1	VEGFR-3	C-Kit	PDGFRB	c-Raf	b-Raf	Src	Flt-3	FGFR-1	EGFR
Vatalanib	III	2	18	13.5	13.5	-	-	-	-	-	-
Sorafenib	III	-	0.1	0.53	0.3	0.07	0.24	-	0.64	6.4	-
Sunitinib	III	≤ 1	≤ 1	≤ 1	≤ 1	-	-	-	≤ 1	90	10,000
AZD-6474	III	40	-	-	27.5	-	-	-	-	90	12.5
CP-547632	II	-	-	-	79	-	-	-	-	0.8	545
CEP-7055	I	0.8	1	-	-	-	-	-	0.3	27	-
Axitinib	I	1.4	-	0.5	≤ 1	-	-	-	-	12.8	-
GW-786034	I	5	1	-	-	-	-	150	-	-	590
Chir 258	I	1	1	0.15	2	-	-	508	0.008	1	169

Courtesy of Renzo Canetta, Bristol-Myers Squibb

The compounds in the left column are all designed to block VEGFR-2. The data show how selective each compound is for a range of other tyrosine kinases compared to its intended target (fold-selectivity vs VEGFR-2)

survival benefit was significant at p=0.001.

Bob Milsted, AstraZeneca's global head of regulatory affairs for oncology, accepts that there is a problem getting the science right, but he stresses that people must have realistic expectations about what can be achieved within a given time period. He argues that it will always be the case that when a new drug is ready for the market, researchers will only just have begun to understand how it works, and he points out that methotrexate, which is targeted at a specific enzyme, has been on the market for a good 40 years and there are still no validated biomarkers to indicate which patients respond best to it. What many people don't realise about targeted drugs, he says, is that you need a drug capable of hitting a given target before you can start to look at what the effects of hitting that target might be.

"When a new drug appears on the scene it is two things. One is a drug in development. The second is a pharmacological tool. It is not until I have the drug that I can shut down that signalling pathway and see what happens and start to explore the science. That is when I can start to tease out whether the pathway is driving the malignant phenotype in all patients, or only in some of them, and if it is only some, can I recognise them?"

Rachel Humphrey from Bristol-Myers Squibb, cast doubt on whether it would ever be possible to identify precise mechanisms, or indeed to establish whether a given drug is actually hitting its target rather than something else. Tyrosine kinases, for instance, are all so similar in structure, she said, that it is very likely that whichever pathway you aim at, you will end up blocking other pathways as well, and there is no way of knowing which is the pathway of greatest significance. The best chance of progress, she suggested, now lies in using combinations of inhibitors aimed at multiple targets.

Missing the target

What does this mean for our dream of the perfectly targeted anti-cancer drug? Jan Liliemark from the Swedish Medical Products Agency found Humphrey's message realistic but depressing. "For a drug that hits 20 different kinases or pathways, there is no point in investigating precisely how it works. There is no reason to believe that we can tell for each patient what this drug is actually doing or not doing." But his colleague Bertil Jonsson emphasised that this does not mean we give up trying to understand. "I believe it is our duty to try to understand what is happening. Of course we will always make mistakes, but a purely empirical approach cannot be the way forward."

Industry representatives, however, seem fairly relaxed in the face of this dawning recognition that we may never know the precise mechanism of drugs. A senior executive from Merck (KGaA) voiced strong optimism about the potential of intelligent combinations of targeted drugs. Merck, he said, is already working with other pharmaceutical companies to test the effectiveness of approved drugs used in combination. One example is a trial of Erbitux (cetuximab) used in combination with Iressa.

Issues of commercial confidentiality, competition and legal liability, once seen as serious obstacles to cooperation, are being circumvented by using non-commercial third parties – in this case it is José Baselga's team

You need a drug capable of hitting a given target before you can look at the effects of hitting it

in Barcelona that is doing the work. Interestingly, Merck is also looking at combinations in which either one or both of the drugs are still in phase I or II (within their own development pipeline). One example is an angiogenesis inhibitor still in development, which had shown unimpressive clinical response in phase II. "We asked the German Cancer Centre in Heidelberg to do some clinical models combining this drug with Erbitux, and they were extremely excited about the synergistic effects," he said.

The new approach to drug development has had a profound effect on the approval process. As targeted drugs tend to be far less harmful than traditional cytotoxics, there is pressure on the regulators to speed up their decision making.

Raj Puri from the US regulatory body the Food and Drug Administration (FDA) talked about new guidelines issued in April 2005, designed to make it easier for drug developers to obtain important pharmacokinetic information at a much earlier stage of development. Using the new 'exploratory IND [investigational new drug] studies', US investigators can now combine preclinical data with 'first-in-human data' (phase 0) to help them select the most promising drugs before moving into phase I/II trials.

"Rather than doing a full phase I trial, they are directed towards pharmacokinetics and pharmacodynamics as a way of getting into clinical trial. They can gain insight, for instance, on how to dose, based on preclinical data. This option was not open to them before," said Puri.

Questions were also raised about whether regulators are right to withhold approval of a drug that carries low risk and had been shown to be of value to some patients, even when the benefit failed to reach statistical significance at phase III. Milsted said that the phase I/II evidence of a response to Iressa in some patients was so dramatic that when he received the CT scans he asked whether there was any doubt about the original diagnosis, because "the tumour looked more like a lymphoma than NSCLC." He believes this should have been enough to tip the balance in favour of approval, despite the phase III survival figures falling just short of significance.

Conditional approval?

A number of delegates pointed out that the FDA had in the past granted approval on the basis of phase II results alone, under their 'accelerated approval' procedure, and asked why the same could not be done in Europe.

Jonsson from the Swedish Medical Products Agency replied that Europe is generally more cautious in its approach to novel medicines than the US, and he defended EMEA's approach, arguing that the FDA is itself uneasy about the way accelerated approval has worked in practice.

EFFICACY PROFILES IN RENAL CELL CARCINOMA: ANTIBODIES (Abs) vs TYROSINE KINASE INHIBITORS (TKIs) vs COMBINATION

Agent or Combination	Known Targets Inhibited	Observed Objective Response Rate (Phase II)	Observed Rate of "Clinical Benefit" (CR+PR+SD) (Phase II)
Bevacizumab (Abs)	VEGF	10%	-
Gefitinib (TKI)	EGFR	0%	38%
Sorafenib (TKI)	Raf, VEGF, PDGF, Flt-3,	14%	(Ph III: PFS doubled) 89%
Sunitinib (TKI)	VEGFR, PDGF, Flt-3, c-KIT, FGF	40%	68%
Axitinib (TKI)	VEGFR, PDGF	40%	86%
Bevacizumab plus Erlotinib (combo)	VEGF plus EGFR	21%	86%

CR, complete response; PR, partial response; SD stable disease. Courtesy of Rachel Humphrey, Bristol-Myers Squibb

Intelligent combinations of monoclonal antibodies and tyrosine kinase inhibitors may be the way forward

This secluded spot in the Austrian Tyrol provides the perfect setting for informal discussions between industry, academics and the regulators

The procedure was introduced to give patients with serious or life-threatening diseases quicker access to drugs that appear to offer a meaningful improvement over anything already available. The applicant has to demonstrate that their drug has an effect on a surrogate endpoint that is 'reasonably likely to predict clinical benefit', and approval is granted only on condition that further studies are done to verify that the predictions of clinical benefit are borne out by the evidence. However, the FDA have found poor compliance with the conditions, because once the drug is on the market, it is not in the interests of the company to devote its resources to further research – particularly if that research indicates the drug is not as effective as predicted, or is effective only in a very limited group of patients. Though the FDA has the right to take the drug off the market if that research is not done, or indeed if the drug turns out to be less effective than predicted, this has proved hard to do in practice.

Jonsson said that while he recognised that the biggest hurdle for effective drug development is identifying good predictor markers, if the regulators allow too many drugs through without insisting that the company first identify how their drug can be used to best effect, the market could fill up with very expensive drugs that have only marginal clinical benefit in an unselected patient population, and there is a danger that faith in the whole system will collapse. He said that EMEA would soon have similar powers to the FDA to grant conditional approval, and that there needs to be a lot of discussion about how these powers should be used.

Some voices argued that it may be only after the drug has been widely

New FDA guidelines aim to make it easier to obtain vital pharmacokinetic information much earlier

"I don't understand why they don't use tissue samples more to come a bit closer to the real cancer"

used for a number of years that it becomes possible to define which patients respond the best. They made the point that, had Iressa failed to get approval in the US and Japan as happened in Europe, then the information we now have about the particular mutation that predicts a strong response would quite possibly never have come to light.

One delegate came up with a novel suggestion for giving trials teams access to previously untreated patients on the scale needed for more detailed phase II analysis. As a molecular response is often apparent within days, they argued, it should be possible to administer the drug in the neoadjuvant setting to newly diagnosed patients during the normal waiting period between diagnosis and surgery.

Another suggested that if response could be detected so quickly, even if companies had failed to identify which patients would be most likely to respond, every patient could be given the chance to try all possible drugs at least for a week or so, without too great a burden on health budgets.

Commenting later on the whole discussion, Milsted said, "The idea that we can solve all the problems in a few years is unrealistic. But some academics and regulators don't understand that. They say 'You must have developed a biomarker that will tell me who will benefit from this drug.' And you have to say, 'I'm sorry but the science is not available for us to do that. We can only start to do that now because we have treated 3000 patients and we have some data.' "

Jonsson, however, clearly believes companies could do more in phase II to analyse how their drugs perform in real tumour tissue, and said he had taken the opportunity provided by the conference to have an informal discussion with delegates from one of the companies about the use of breast tumour samples.

"I don't understand why the company doesn't use them more to come a bit closer to the real cancer," he said. "You can only treat a patient with one compound, not ten. In a laboratory, however, you can treat the cells with ten compounds and look for markers and look for activity.

"Perhaps from these in-vitro experiments you can find the phenotype that makes it more likely that you have activity."

The problem, he said, lies not so much in the logistics of setting up good-quality tissue banks, but getting access to that tissue – not just for academics but for the industry as well.

Approving combinations

But it is when we start looking at the approval process of combination therapies that things get really complex. Would two drugs approved for use separately need to go through a separate approval process to be used in combination? Yes they would, said the regulators, because we need to know both the combined benefits and the combined side-effects.

What about combining experimental drugs? Would each drug have to be approved for use separately before approval could be sought for the combination? If so, what if one or both the drugs proved too toxic when used alone, but were far less toxic in combination?

Hmm… said the Swedish regulators. We'd have to see the data. If there are clear benefits for patients, we should be able to find ways to resolve the regulatory issues. However, no drugs developer has yet been brave enough to come forward with a test case, so we can't say….

So what about Merck? Would they be up for trying a test case? "I am encouraged at least by the Swedish authorities," said a Merck executive. "I think with these authorities we can talk, and as they mentioned, go for scientific advice. You would not go all the way through phase III trials, and then go and ask them to approve. You would do it stepwise. Initially share the concept. Then ask specific questions, where you get scientific advice. Then come back when you have data. And then discuss the phase III design. It needs a dialogue always."

That dialogue, and step-by-step approach, is exactly what the BDA conferences hope to achieve in terms of developing an agreed overall approach to effective drug development. When it meets again in March 2007, lessons from the first trials of combinations of exploratory drugs, and an assessment of the use of EMEA's conditional approval instrument will be two topics that are likely to find a place on the agenda.