basic science — from cell growth and death to DNA repair and replication — as well as clinical trials, epidemiology and medical statistics. The ICRF and CRC cover all these areas, but there are also many smaller, more specialist charities. These many institutions have one common aim, however — to turn scientific advances into effective ways to prevent or treat cancer. □

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Therapeutics: a glimpse of the future

Owen Goldring

Cancer therapeutics has, until recently, been out of fashion — being seen as an applied rather than an academic discipline. But that is changing, thanks to advances in the understanding of the molecular nature of cancers, coupled with the hot debate centred around telomerase and the initial unravelling of the mechanisms of angiogenesis. A radical new generation of anti-cancer drugs should ensue.

The focus is on discovering small-molecule mechanism-based inhibitors that selectively target or starve cancers. There is a belief that there will be a first generation of *ras* farnesylation inhibitors, receptor tyrosine kinase inhibitors, and possibly p53 drugs, in the next five years (*ras* farnesylation and EGF receptor tyrosine kinase inhibitors are already in phase I clinical trials). Almost up with those will be the first angiogenesis inhibitors. The predictions are that cell-cycle inhibitors will be the next, with apoptosis after that. Telomerase inhibitors may come within five or ten years.

But, given that cancer is basically a disease of an unstable genome, some scientists believe that cancer will develop resistance to any drug thrown at it. They feel that more research is needed now to look at resistance mechanisms.

Search for selective drugs

There will be no sudden development of a 'pan-cancer' drug — the opposite will probably be true, with selective molecular drugs of high therapeutic index being used against specific solid tumours. Neither will conventional anti-cancer drugs, such as methotrexate and cyclophosphamide, be replaced overnight. But every researcher would like to offer a treatment that is more selective and considerably less toxic.

Drug discovery programmes are using techniques such as random screening for finding chemical leads, or structural rational design, where structural biologists use NMR and crystallography to figure out the molecular interaction between a target and an inhibitor (see *Anti-Cancer Drug Design* **12,** 525–531; 1997). These methods require a new breed of cancer scientist.

Paul Workman, the new director of the CRC Centre for Cancer Therapeutics, at the Institute of Cancer Research's labs in Surrey in the United Kingdom, says that, before the advent of molecular oncology, there was a cultural, ideological and skill-capability misfit between cancer biologists and those making derivatives of methotrexate. These two schools did not speak the same language. Now, they are beginning to, he says.

So, what skills do you need if you want to get into cancer therapeutics today? Workman says the type of scientist that biotech companies and even some major pharmaceutical companies lack is what he calls the "cancer pharmacologist". "These are not 'general' pharmacologists who are brought into a cancer project, as occurs in some companies. They are people who live and breathe cancer pharmacology, understand cancer pathways and can apply their pharmacological skills to these new molecular opportunities. They will not necessarily have cloned genes, but I do expect them to be able to do PCR, western blots, northerns, Southerns and so on." They need to understand the language of molecular biology, and traditionally trained pharmacologists tend not to have these skills, Workman says.

Two types of people are needed: those who have done biological science degrees, molecular biology, biochemistry, and then learn pharmacology; and those trained as traditional pharmacologists, because they bring a familiarity with concepts such as dose-response relationships and kinetics, says Workman. "Most molecular biologists have no training in these critical aspects of pharmacology. You need both. And you also need people trained in pharmacokinetics."

Angiogenesis link to mutation?

Each tumour needs to develop its own blood supply, says Roy Bicknell, head of the Imperial Cancer Research Fund's angiogenesis lab in the Institute of Molecular Medicine at John Radcliffe Hospital, Oxford. "Small tumours remain dormant until they undergo an angiogenic switch, when they start making angiogenic factors, and then recruit in new blood vessels. The tumour then grows rapidly. There is evidence to suggest the angiogenic switch is linked to a mutation in p53," says Bicknell.

Bicknell apparently does not mind which areas of science his PhD students come from: "They must be bright and inquisitive but, as long as they are practically adept, we reckon we can fill in any gaps in theoretical knowledge." One of his students has a first-class degree from Cambridge in zoology, another is a veterinarian from Germany, and a third has a medical degree from Oxford University.

Another, somewhat controversial, area of cancer therapeutics is telomerase inhibition. About 85% of tumour cells produce telomerase, which keeps telomeres stable, and the assumption has been that cancer cells need telomerase to maintain continuous cell division.

Geron, a company based in Menlo Park, California, is studying the genetic clock of cell ageing, telomeres and telomerase. Geron has a substantial programme of research on telomerase inhibition (see Table 1).

Bioengineering angle

One possible route for future work on telomerase and angiogenesis is offered by Martin Braddock, leader of the endothelial gene expression group in the vascular diseases unit at Glaxo Wellcome's Stevenage labs in southern England: "When we expose endothelial cells in culture to fluid shear stress (for example, mimicking what happens with arterial blood flow), we have evidence that functional telomerase activity is downregulated." He encourages people to think about coupling telomerase activity with biomechanical forces, and relating that to cellular processes in angiogenesis.

"I think that's the way angiogenesis is going to go in the future," he says, adding that it will be understood almost from a bioengineering angle rather than from a purely cell or molecular biological angle. "We're almost at the start of the era of tissue engineering."

Cancer therapeutics is an area where the opportunity for doing exciting and groundbreaking research is very much on the up. But one problem that researchers will face — at least in Europe — is the dearth of second postdoc positions to enable them to get greater experience and a step further up the ladder to landing that elusive permanent academic job.

Many high-flyers gravitate from Europe to the United States after a first postdoc, do more academic research and then sometimes spend time in the biotech industry before returning to Europe. They are often welcomed back with open arms, being seen as having demonstrated an entrepreneurial outlook as well as having enhanced their academic experience.

Few people automatically turn to industry straight after a PhD or postdoc, perceiving that in industry people have to change subjects often. But this may be a misconception. Glaxo's Braddock says: "In our own particular area of research at the moment we are productive, and I hope that will remain so. If we hadn't been productive over the last few years we wouldn't work on it. But if we were in a university lab and non-productive, and had no grants to write after three years, the same situation would apply." □

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