Action at the edges in cancer research

Hopes that therapeutic advances are just over the horizon are bringing increased funding to cancer research. Scientists joining from a variety of fields should find an environment very different from that of the past decade.

Potter Wickware

In cancer research, the scientist can productively study almost any area of basic biology, whether it be signalling, apoptosis, motility, membrane synthesis or structural biology, says Daniel Louvard, research director of the Institut Curie in Paris, and an investigator of membrane interfaces. Researchers have begun to discern simple unifying principles underlying the intricate complexity of the course of the disease in individuals.

The atmosphere in cancer research today owes much of its excitement to the growing understanding that cancer mechanisms are both diverse and unifying, and that the apparent contradiction is resolvable, says Louvard. As we now realize, it is some finite and knowable number of misbehaving biological processes combinatorially relating to one another in a malignant clone that produces the individual disease profile.

"We're developing a new way of thinking about biology that will lead to real advances. This is one of the compelling attractions of cancer research in the period we are entering," says Louvard. Scientific understanding combined with remarkable technological advances brings us closer to delivering better diagnosis and treatment. Innovations such as the DNA gene chip array, a technology being developed by Affymetrix of Palo Alto, California, and others, will allow the construction of a complete catalogue of a patient's genetic activity. Treatment can be tailored from that, based on profiles of which genes are behaving normally and which are aberrant.

New ways of thinking

Thea Tlsty, who studies genetic instability in breast cancer cell lines at the University of California in San Francisco, shares the excitement about the new avenues of investigation now opening up. One example is the use of *trans*-retinol as an antineoplastic agent. "Instead of using poisons to kill the cell and straining to mitigate side-effects in healthy cells, this approach causes cancer cells to, in effect, differentiate themselves out of existence," she explains. It has become important in clinical use, and is just as significant as an intellectual concept, in showing a new way to think about cancer.

To explore and exploit new ideas, Tlsty says the cancer researcher ought to have competence in imaging, bioinformatics and computing, as well as in the biological and chemical basics. Yet it is a mistake for a scientist to think too closely about techniques, because in research the relationships between different regions of enquiry change rapidly. "These relationships are like droplets trying to coalesce. All the action is at the edges. Suddenly the two come together and there is no more interface — or rather there is a new interface that pops up somewhere else." For the student contemplating a career in cancer research, or any area of biology, the point is to develop the ability to think analytically, to formulate the query, and to plan an experimental strategy that will work. These skills never lose their relevance, no matter what the experimental context.

But what about the Malthusian crisis of expanding numbers of PhDs chasing limited numbers of faculty positions and grants? "Only by taking a narrow view of a scientific education do you run up against a limit in cancer research," says Tlsty. "The number of faculty slots in universities is limited. But there are many other areas: government, consulting on environment and hazards, research and development in industry, writing, tutoring venture capitalists, patent law. And the cancer research world is changing so rapidly that the educational and interpretive roles of the scientist are becoming especially important."

Tomorrow's challenge

Louvard also sees opportunity as he gazes into the future of cancer research, but cautions that progress will depend on an intellectual reorganization. "We have become adept at dissecting a problem into its component parts, but now we have learned to put the pieces back together. To do this we'll have to improve communication among the participating disciplines. This is the great challenge of tomorrow."

Cancer research awaits those who, like the group which catalysed the revolution in molecular biology a generation ago, have the ability to connect apparently unrelated findings and see the world in some fundamentally different way. "Perhaps it will be the physicists again," Louvard speculates. □

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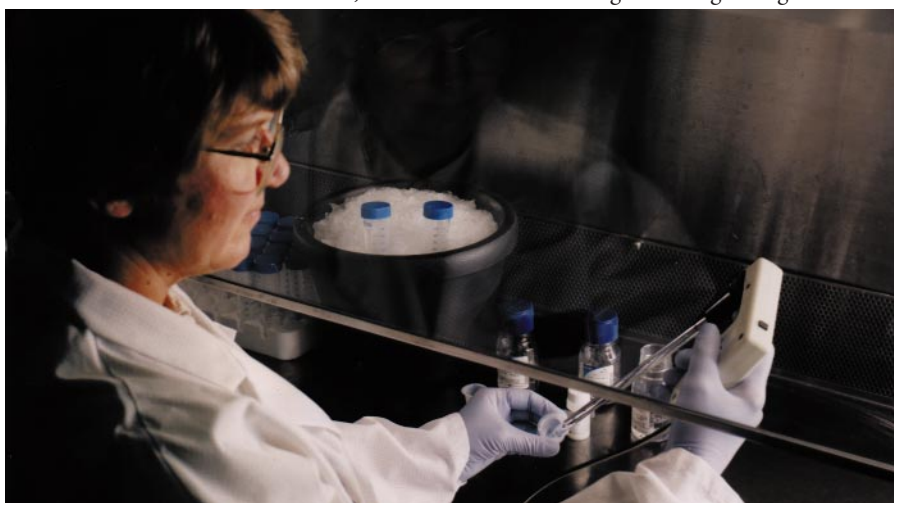
Seeking the bigger picture in the puzzle

Brendan Horton

Last December, Human Genome Sciences (HGS) of Rockville, Maryland, announced that it had applied to start phase I clinical testing of myeloid progenitor inhibitory factor-1. This compound, according to HGS, may allow oncologists to treat cancer patients with far more potent doses of chemotherapy. Screened from 300 full-length genes, this human protein has been shown in preclinical trials to "shield haematopoietic progenitor cells in the bone marrow from the effects of a number of chemotherapeutic agents used to treat all major cancers". HGS thinks the factor works by inhibiting proliferation and differentiation of these cells. Company chairman William Haseltine believes this to be the first genomics-derived therapeutic candidate to enter clinical testing. It will not be the last.

Not far from HGS, on the campus of the National Institutes of Health, the National Cancer Institute (NCI) has created a programme to advance the use of genomics and other technologies in diagnosing and treat-



LIFE TECHNOLOGIES

Preparing a cDNA library: these will be a storehouse of genetic information for cancer researchers.

ing cancer. When Richard Klausner, now in his third year as NCI's director, joined the institute he took a broad look at its research funding and asked what could be done differently. According to his assistant, Robert Strausberg, five areas had little or no investment, so were all 'rescued' via the institute's bypass budget. These were cancer genetics, developmental diagnostics, detection technology, preclinical model development, and interfacing basic and clinical research (so-called translational research).

Table 1 Sites of Internet interest for cancer research

Site name	*URLs: http://*
General	
NCI's Cancer Genome Anatomy Project	www.ncbi.nlm.nih.gov/ncicgap/
The National Cancer Institute	www.nci.nih.gov/
Human EST project	genome.wustl.edu/est/esthmpg.html
NCI's technology transfer fellowship programme	www.nci.nih.gov/ttran/ttfp/ttf.htm
Lawrence Livermore National Lab/IMAGE Consortium	www-bio.llnl.gov/bbrp/image/image.html
Corporations	
Human Genome Sciences	www.hgsi.com/
Life Technologies, Inc.	www.lifetech.com/
Stratagene	www.stratagene.com
Geron	www.geron.com/
Arctur	www.arctur.com/
Academic	
Patrick Brown's lab, Stanford	cmgm.stanford.edu/pbrown/
Stanford's Genome Resources	genome-www.stanford.edu/

Genome anatomy project

Work groups were set up by Klausner to look at new ways to use cancer funding. From the developmental diagnostics group came the idea for a cancer genome anatomy project (CGAP). According to Strausberg, the group was dissatisfied that, despite much progress in learning about genes over the past ten years, the bigger picture was still missing from the cancer puzzle. They saw "an opportunity to take advantage of advancing technologies and genome resources in defining the complete molecular anatomy of cancer cells and their precursors," says Strausberg. The idea was to identify the best fingerprints that distinguish one cancer from another, as well as to differentiate the stages of cancer progression, even for "tumours that look identical histologically, but are different at the molecular level and respond differently to treatment".

Last year, two steps were taken towards making CGAP a reality. Both used funds from NCI's bypass budget. (The projects have since been written into this year's fiscal budget.) The first step was the creation of the tumour gene index, designed to house all the genes that are expressed during tumour development, covering the range from normal to precancerous and cancerous cells. Initially, five tumour types are being included: breast, prostate, lung, colon and ovarian.

Of primary importance to NCI is to put this information into the public domain as soon as it is received and verified. The dissemination of information and other resources is performed in collaboration with the IMAGE consortium project of cDNA library sequencing to find the expressed genes.

According to David Krizman, a molecular biologist in NCI's pathology laboratory, this technology is not yet highly evolved. It started with basic, pre-existing technology. Over the first six months, sources of cDNA libraries have included the NCI laboratory, Life Technologies of Gaithersburg, Maryland and Stratagene of La Jolla, California, as well as Bento Soares' laboratory at the University of Iowa. The libraries are arrayed at Lawrence Livermore National Laboratory, followed by sequencing at Washington University. To date 170,000 sequences have been deposited in GenBank by the CGAP project. Mapping of expressed sequence tags is performed by Stanford Genome system using radiation hybrid panels.

Construction of cDNA libraries is the near-term goal for CGAP, says Krizman. The longer-term goal is to increase usefulness through longer, more efficient inserts and to develop cost-effective, high-throughput, full-length cloning.

The second important aspect of CGAP is to create mechanisms for development of technologies that achieve "comprehensive high-throughput molecular analysis of gene and protein expression, as well as [techniques for] mutation detection". An early example is the development of the laser-capture microdissection (LCM) technique by Lance A. Liotta and colleagues at NCI. This allows the dissection of pure cells from different stages of cancer development, and permits libraries to be made that reflect these stages (see Table 1 for CGAP Web page).

Strausberg says it is important to make this technology available to the entire community and, for this reason, the technology transfer was rapid. It was commercially developed as the PixCell LCM system through a Collaborative Research and Development Agreement partnership with Arcturus Engineering (see Table 1).

Table 2 Recent funding announcements from the NCI, the National Human Genome Research Institute (NHGRI) and the National Institute for Standards and Technology

1) High-throughput technologies to detect alterations in tumours http://www.nih.gov/grants/guide/pa-files/PAR-97-021.html
2) Novel technologies for evaluation of molecular alterations in tissue http://www.nih.gov/grants/guide/rfa-files/RFA-CA-97-011.html
3) The development of genomic-scale technologies, or implementation of pilot-scale or large-scale projects for the discovery and scoring of single nucleotide polymorphisms http://www.nhgri.nih.gov/Grant_info/Funding/rfa-hg-98-001.html
4) The development of a network for large-scale sequencing of the human genome http://www.nhgri.nih.gov/Grant_info/Funding/rfa-hg-98-002.html

Future studies and technology

In addition to developing a wide variety of technologies for investigating changes in genes and their expression, an initiative has been announced that will create an interface between the technology developers and the clinical researchers (see Table 2). "As the technologies are being developed, we want researchers to think about the kinds of questions that could be answered with them," says Strausberg. One of NCI's main objectives is to build interdisciplinary teams of technology developers, including molecular biologists, engineers, physicists and cancer researchers, so that a complete system for analysis will be created.

Researchers would like to be able to trace the contribution that various genes make to the development of cancer. One aspect is identifying polymorphisms of genes that will allow the inheritance of the genes to be followed, says Strausberg. The NCI is building this capacity into the CGAP system, including the ability to identify and catalogue single nucleotide polymorphisms. "This is challenging and we are evaluating the technologies to do this efficiently," says Strausberg.

The institute is also beginning a mouse CGAP project as part of a programme to evaluate and standardize model organisms, as well as to look at analogous tumours between mice and humans for comparative analysis. Other technologies on the horizon, says Krizman, are those that allow investigation of mutation analysis, such as finding single-point mutations within coding sequences.

"There is an enormous opportunity, which we started catalysing last year with the NCI funds," says Strausberg. "You would like to gain more than just a few snapshots of the cancer, and to understand this as a dynamic process, to understand the events that happen in the transition from a normal cell to a cancer cell. We need to be able to look at

single cells, not merely populations of cells." This requires further development of the technology. For CGAP, having the funds and the ability to bring in a wider community of technology developers to work on these problems should expedite this process. □

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Visionaries seek UK national strategy

Alison Mitchell

The Imperial Cancer Research Fund (ICRF) has a vision. By 2020, it believes that considerable advances will have been made in the prevention, early detection and treatment of cancer. But it cannot achieve these goals alone and, last month, it supported calls for a national strategy on cancer research — a collaboration between the UK government, the research charities and industry.

At present, charity research institutions cannot freely apply to government research agencies for support. Paul Nurse, director-general of the ICRF, says: "Government funding needs to be more flexible, to ensure that resources are spent where they can be best used." The stumbling block seems to be that government grant-awarding bodies allocate only a small percentage of their budgets to cancer research precisely because the cancer charities exist. But links are being forged between the charities and industry, and such schemes may provide opportunities for students, postdocs and group leaders.

The ICRF is the largest UK cancer charity, spending £54 million (US$89 million) a year on research, closely followed by the Cancer Research Campaign (CRC) which spends £50 million. The charities distribute their funds very differently. The ICRF runs its own laboratories, while the CRC mainly supports research within universities and medical schools (see box below). How much room do these strategies leave for collaboration?

Plenty, it seems. Because of the way it distributes its funds, the CRC is particularly open to joint research ventures. As well as funding large groups within centres such as the Institute of Cancer Research in London, in 1989 the CRC was one of the partners that set up the Wellcome/CRC Institute in Cambridge. The Wellcome Trust does not fund cancer research, but the scientific focus at this institute is on basic research into the cellular processes that are relevant to development. The ICRF's clinical directorate also has strong research partnerships with the National Health Service trusts. Mike Probert, the charity's assistant director of research, clinical division, says most of the clinical studies "would not be possible without the flow of patients through NHS hospitals".

The charities are also increasingly looking for ways to develop their discoveries commercially. The ICRF's technology transfer arm, Imperial Cancer Research Technology (ICRT), bridges the gap between basic research and product development. Last October, in a joint venture with the pharmaceutical company Antisoma, ICRT announced a phase III clinical trial of Theragyn. This drug is based on a murine monoclonal antibody developed by ICRF scientist Joyce Taylor-Papadimitriou and colleagues. The antibody is chemically linked to a radioactive isotope, yttrium-90, which is targeted to cancer cells. Phase I/II trials showed it to be particularly effective in patients with ovarian cancer.

Marketing teamwork

The CRC's technology transfer company is Cancer Research Campaign Technology (CRCT) which announced last month that it was teaming up with the UK company Serotec to market immunological reagents developed by the CRC. Another venture is Oncotech, which aims to develop the commercial potential of cancer research. This is a consortium of CRCT, the Leukaemia Research Fund, the law firm Cameron McKenna and the patent firm Mewburn Ellis.

So, in many ways, a national strategy for cancer research may not be very far away. Indeed, the ICRF and CRC already belong to a joint venture with the Medical Research Council and the Department of Health. But cancer research encompasses many areas of

Table 3 Sites of Internet interest for UK cancer research

Site name	*URLs: http://*
General	
ICRF	www.icnet.uk/public.html
CRC	www.crc.org.uk
Leukaemia Research Fund	dspace.dial.pipex.com/lrf-//
Academic	
Gray Laboratories	www.graylab.ac.uk/
CRC Beatson Laboratories	www.vet.gla.ac.uk/beatson/
Institute of Cancer Research	www.icr.ac.uk/
Marie Curie Research Institute	mc11.mcri.ac.uk/mcrihome.html
Paterson Institute for Cancer Research	christie.man.ac.uk/picr.htm
Ludwig Institute (UCL)	www.ludwig.ucl.ac.uk/
Ludwig Institute (St Mary's)	www.sm.ic.ac.uk/ludwig/
Corporations	
Serotec	www.serotec.co.uk/

Research opportunities at the cancer charities

Research at the ICRF is broken down into basic science, clinical studies and translational research – the middle ground between the two. Most of the basic science is carried out at the laboratories in central London and at Clare Hall in Hertfordshire.

These sites employ around 80 graduate students and 180 postdocs. Students usually receive funding for four years from the charity, and must register externally for a PhD.

About 30 postdoctoral fellowships are available each year in basic research. For those bringing their own grants, the ICRF offers access to support services (including cell and media production, oligonucleotides, instruments and antibodies). Recruitment of group leaders has slowed after big campaigns in the last two years, but positions are available.

Clinical research units are based in hospitals and medical schools around the United Kingdom, covering areas ranging from immunotherapy to breast oncology. A total of 33 graduate students is funded by the ICRF, plus 44 clinical fellows and 49 postdocs.

The CRC divides its research between basic and clinical studies in a roughly 45:55 split. It awards grants to groups at the Paterson Institute in Manchester, the Beatson Institute in Glasgow, the Institute for Cancer Research and associated CRC centres, the Gray Laboratory Cancer Research Trust in London, and groups at universities such as Birmingham and Dundee.

Seventy-six students are funded by the CRC. Training follows guidelines set by the host institutions.

The CRC runs three fellowship schemes – Research Fellowships for Clinicians, Senior Clinical Fellowships and Senior Cancer Research Fellowships. Between them, these support 597 postdoctoral fellows. Scientists can also apply for project grants, which are reviewed by the grants committee four times a year. The Wellcome/CRC Institute operates junior and senior research groups, with the junior groups staying for a maximum of ten years.

Both charities are developing 'translational research', to bridge the gap between basic and clinical research. The ICRF has a training scheme in this area, which is now in its third year, with ten clinical or postdoctoral fellows. **A.M.**