

Meeting report

The application of basic science to translational cancer research

Paul Ko Ferrigno

Address: MRC Cancer Cell Unit, Hutchison/MRC Research Centre, Hills Road, Cambridge CB2 2XZ, UK.
E-mail: pkf@hutchison-mrc.cam.ac.uk

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A report on the inaugural symposium of the Hutchison/MRC Research Centre, Cambridge, UK, 24-25 October 2002.

The Hutchison/MRC Research Centre was formally opened this year. Its goal, as stated on its website [<http://www.hutchison-mrc.cam.ac.uk/>], is to bring basic research into the practice of clinical oncology, and groups in the Centre (including my own) hope, for example, to use an understanding of the basic machinery of DNA replication and state-of-the-art genomic technologies to screen for new mutations that lead to a predisposition to cancer. Yet fundamental questions about this strategy remain: whether we understand enough biology to design anti-cancer strategies, whether translational research belongs in the academic setting, what the impact of genome-wide studies will be on cancer diagnosis and treatment, and whether scientists can now deliver on their promises to medicine.

What causes cancer? It has taken us nearly 40 years to provide a partial answer to this superficially simple question. A consensus is emerging that, more often than not, a combination of events is required for cancer formation: the gain of expression of an oncogene that directs the cells to divide, the loss of tumor suppressors that would otherwise inhibit signals to replicate or guard the integrity of the genome, and/or a defect in DNA replication or DNA repair.

The basic biology of cancer

The cell cycle

It has sometimes been assumed that all we need to know about the biology of cancer can be learnt from studies of the biology of the cell-division cycle. Tim Hunt (Cancer Research UK, Clare Hall, UK), one of the people who have driven cell-cycle research, gave a presentation of the concepts that underlie our understanding of cell proliferation and a description of the molecular machineries that mediate

progression through the cell cycle. He ended, however, with the controversial statement that cell-cycle regulators will not be good drug targets in cancer therapy. Hunt's view is that cancer is a disease of development rather than cell division. Targeting a cell's developmental decision-makers will allow therapies to act specifically on tumor cells, whereas cell-cycle inhibitors will lack specificity, leading to the unpleasant side-effects with which cancer patients are already all too familiar.

Kim Nasmyth (Institute of Molecular Pathology, Vienna, Austria) was one of many speakers whose work suggests that cell-cycle regulators are certainly worth investigating. He described the molecular machinery that triggers the release of sister-chromatid cohesion at the onset of anaphase. Nasmyth used an apt analogy to describe the intricate problem of getting each set of homologous chromatids to opposite ends of the dividing anaphase cell: two blind men separating two sets of five pairs of colored socks, with each man wanting to end up with five pairs of socks, one pair of each color. Like the cell, the blind men solve the problem by each taking one sock (chromatid) from each pair, but whereas we can understand how they achieve this, we have some way to go to understand how the cell manages the analogous feat. Nasmyth described some very nice experiments in yeast showing that each pair of sister chromatids created by DNA replication in S phase are embraced by a ring formed from the four-subunit protein complex called cohesin. The trigger for separation seems to be the degradation by the anaphase-promoting complex of securin, an inhibitor of a cohesin protease called separase. He showed that insertion into cohesin of sites for proteases other than separase, and cleavage of these inserted sites, is sufficient to cause the separation of homologous chromatids in yeast cells. Clearly, any defect in chromosome partitioning that allows a daughter cell to acquire fewer or more copies of each region of the genome will potentially allow that cell to lose a tumor suppressor or gain an oncogene. The molecular details of anaphase differ between yeast

and humans, but many of the proteins that regulate or monitor sister-chromatid separation are known to be altered in human cancer cells, suggesting that this pathway may represent a new route to therapies.

DNA damage

How does DNA damage contribute to the very first steps in cancer? The work of Susan Gasser (University of Geneva, Switzerland) addresses the machineries behind this fundamental question, focusing on the intra-S-phase checkpoint. Checkpoints within the cell cycle serve to ensure the completion of one process before the next begins; the intra-S-phase checkpoint prevents DNA replication through damaged DNA. The very existence of this checkpoint has been hard to prove, and it was really only hinted at because of the defective activation of other, G₂/M phase checkpoints in cells harboring specific mutations in genes that regulate S phase. Gasser has provided compelling evidence for the existence of the intra-S-phase checkpoint and has begun to dissect it at the molecular level. She explained that Orc2p, one of the proteins responsible for loading the DNA-replication machinery onto DNA, is required for the phosphorylation of the checkpoint protein Rad53 when DNA is damaged during S phase. This phosphorylation can still occur in Orc2-deficient cells when the DNA-damaging treatment is applied in G₂ phase, suggesting that the phenomenon really is an intra-S-phase event.

At the molecular level, stalled replication forks closely resemble damaged DNA. Why then doesn't the cell respond to cut DNA at replication forks as it would if the DNA were genuinely damaged? We know that stalled replication forks trigger the intra-S-phase checkpoint, whereas DNA damage would trigger the G₂/M-phase checkpoint. Gasser's data suggest that the threshold for G₂/M checkpoint activation by DNA damage is lower than the threshold for activation of the intra-S-phase checkpoint, providing a mechanism that allows cells to proceed through S phase even though replication forks could be confused with damaged DNA. The intra-S-phase checkpoint signal appears to originate at the replication fork, and Gasser showed data implicating the DNA helicase Sgs1p as a stabilizer of DNA polymerases at stalled replication forks, perhaps acting by maintaining the single-stranded DNA template. A human homolog of Sgs1p has been implicated in aging processes, as it is mutated in Werner's Syndrome, an aging syndrome that includes a predisposition to cancer. It will be particularly interesting to know whether the molecular basis of Sgs1 function is the same in aging and in cancer.

Jan Hoeijmakers (Erasmus University, Rotterdam, The Netherlands), who has also been instrumental in furthering our understanding of the links between DNA repair and cancer, similarly hinted at a link between aging (senescence) and cancer. The studies of his group have focused on relatively rare human genetic syndromes such as Xeroderma

Pigmentosum, trichothiodystrophy (TTD) and Cockayne's syndrome, all of which predispose to cancer. The genes whose mutations lead to these diseases have generally proved to encode proteins that normally participate in nucleotide-excision repair of helix-distorting DNA damage. The most recently studied of these proteins, those involved in TTD, may also provide a link between DNA repair and aging. Hoeijmakers suggested that this may be due to decreased cell function following loss of transcription caused by inappropriate handling of transcription-blocking DNA damage in TTD cells, leading to cellular senescence.

DNA synthesis

The spatial and temporal control of DNA synthesis was described by Ed Harlow (Harvard Medical School, Boston, USA). Using primary cells, rather than the cultured cell lines that are most often used for this type of study, Harlow showed that bromodeoxyuridine (BrdU) can be used to mark foci of DNA replication in the nucleus. Such sites have been missed previously, at least in part because the immortalization of cells required to produce a cell line alters the pattern of DNA replication: in fact, foci of replication are almost completely lost even in very early passage cells. Harlow also showed that, like BrdU incorporation, the tumor suppressor protein retinoblastoma (pRb) is localized to a few large foci in the nucleus early in S phase (a pattern called the focal phenotype) and in a large number of smaller foci as DNA replication nears completion (the distributed phenotype). Indeed, proteins that interact with pRb, such as histone deacetylases and the transcription factors E2F and p130, all colocalize with the polymerase subunit PCNA at sites of BrdU incorporation in early S-phase nuclei, and this pattern is lost in late S phase.

In an attempt to characterize these pRb/BrdU foci, Harlow turned to a comprehensive list of other proteins known to bind to pRb (published by E.J. Morris and N.J. Dyson in 2001). One such protein is lamin A, a structural protein of the nucleus. When Harlow looked at pRb in lamin A^{-/-} mouse embryonic fibroblasts, the pRb protein was found to be destabilized, although RNA levels were not affected; pRb was not even in the nucleus, indicating that lamin A may have a role in the establishment or maintenance of sites of DNA replication. These could conceivably correspond to DNA replication 'factories', through which replicating chromatin would spool. Like cells containing mutant pRb, lamin A-deficient fibroblasts fail to arrest after γ irradiation, indicating that the presence of pRb at the sites of DNA replication may play a role in checkpoint arrest following DNA damage. Intriguingly, DNA replication may also respond to cell density: in densely grown populations, BrdU incorporation remains focal even late in S phase, in contrast to the previously described situation in sparsely grown cells. If this observed difference reflects a biological reality, it may correspond to a difference between tumor and normal cells that could be exploited in cancer treatment.

Genome-scale analyses and other visionary technologies

Roger Brent (Molecular Sciences Institute, Berkeley, USA) described two approaches that he is taking to look at molecular interactions. First, he outlined the design of completely novel ways of detecting molecular interactions in single cells, so that the contribution of cell-to-cell variability to the behavior of populations of cells can start to be measured. Brent described the work of the 'Alpha project' [<http://www.molsci.org/alpha>], a collaboration between groups at different institutes that has so far used the transcriptional output of the yeast pheromone signaling pathway to measure the effects on signal transduction of perturbations to the yeast cells. Second, Brent has been developing methods for the detection of single molecules of protein. A single molecule of DNA can be reliably detected 3 times out of 10, and a single molecule of RNA can be reliably detected 90% of the time; there has not been any technology that would allow detection of single protein molecules every time. Peptide aptamers are recognition reagents that bind specifically to a given protein. Brent and coworkers have devised a method of covalently linking each peptide aptamer to the DNA that encodes it, creating reagents he calls 'tadpoles'. Because the DNA can be amplified by PCR, this should allow the detection of single molecules of protein, even in complex samples, bringing the sensitivity of protein detection to the levels achieved for the detection of RNA or DNA.

From cancer cells to cancer genes

What can genome-wide studies contribute to our understanding of cancer? Nick Lemoine (Imperial College Faculty of Medicine, London, UK) described the range of technologies available and some of their clinical applications. Laser-capture microdissection can be used to isolate individual cells or small, suspicious lesions from patient samples. The genomes of these cells can then be subjected to mutational analysis, DNA fingerprinting, microarrays or two-dimensional gel proteomic analysis. The goal of these studies is both to devise new ways to classify tumors and to seek clues to the likely response of each patient to chemotherapy. The results can be intriguing; for example, of the 245 genes whose expression changed in response to treatment with the EGF-receptor antagonist Iressa, none encoded the EGF-receptor!

Lemoine then highlighted a bottleneck in drug discovery: the validation of potential drug targets. He described the development of a very elegant approach to inhibiting the expression of individual genes, called Gene ICE. Simply put, triplex-forming oligonucleotides (TFOs) are used to bind specifically to DNA sequences present in the upstream regulatory regions of target genes. Covalently bound to the TFOs are 29 amino acids from the Mad transcription factor that are sufficient to recruit transcriptional co-repressors, including histone deacetylases, leading to gene silencing. This technology should allow us to determine the relevance of any gene changes identified in molecular profiling by

microarrays and also to determine whether any of the altered genes are good drug targets. If Gene ICE cures cellular models of a disease, drugs that target that protein are likely to cure that disease in humans.

'Cancer-omics'

Olli Kallioniemi (now at VTT Biotechnology, Turku, Finland) started by warning us that the 'omics' craze obscures the fact that basic biological discoveries remain key, but then took us on a breath-taking tour of high-throughput technologies for translational cancer research in the post-genomic era. His opening question was: can large-scale profiling lead us to a single validated drug target? His answer was that it probably can, if one first integrates DNA, RNA and protein profiling data to identify the most promising candidates, then uses high-throughput clinical studies to confirm clinical relevance before using high-throughput cell-based studies in hypothesis-driven experiments to validate them. Thus, array comparative genome hybridization (array CGH) can be used to look at genome amplification, while DNA or oligonucleotide microarrays can reveal levels of transcription of candidate genes. In this way, Kallioniemi's group has produced high-resolution overviews of the genomes of breast and prostate cancer cells that have allowed him to identify new amplifications and deletions. This approach detects 90% of the abnormalities seen in conventional CGH but also detects many others that were previously missed. Kallioniemi also briefly described a new technique, in which inhibition of the nonsense-mediated RNA-decay pathway allows the accumulation of transcripts encoding mutated or truncated proteins. This idea has allowed the detection of known truncations in cell lines, but it is not yet known whether it will allow the identification of any novel cancer-associated mutations.

From cancer genes to pathways to cancer

Ed Liu (Genome Institute of Singapore) emphasized the point made by others that large-scale microarray data are more useful in the identification of important pathways than of identifying individual genes. His group has studied thyroid hormone signaling and uncovered an unexpected role for the pathway downstream of the Wnt signaling molecule. His data showed that increased thyroid hormone signaling coordinately decreased activity of members of the Wnt pathway (an anti-carcinogenic effect), while decreased levels of thyroid hormone appeared to increase the activity of the Wnt pathway, which could lead to carcinogenesis. These observations were confirmed biochemically. Consistent with Liu's microarray-driven hypothesis, it has previously been observed that a dominant-negative thyroid-hormone receptor (*v-ErbA*) is carcinogenic in chickens and that mutants of the receptor that cannot bind DNA are frequently associated with liver cancer in humans.

Liu then went on to show that the molecular profiles of tumors can be a signature of the genetic points of origin of the cancer. Using transgenic mouse cancer models, Liu showed that

cancers caused by oncogenes in the same pathway (such as genes encoding Erb-B2, its receptor Neu, and the small GTPase Ras) give rise to microarray profiles that can be clustered together and that are distinct from cancers caused by oncogenes on different pathways (such as SV40 large T antigen and the transcription factor Myc). When examining human breast cancers, he found that the most powerful factor that leads to distinct expression profiles is the presence or absence of estrogen receptor (ER) expression: the expression profiles of ER-negative and ER-positive breast cancers cluster separately. In addition, ER-positive cancers can be divided by molecular profiling into two prognostic groups - one with an excellent outcome and the other with a rate of relapse-free survival only half as high. These observations are remarkably consistent with several other studies, and comparison of the gene lists from different studies identifies specific prognosis-associated genes. This is likely to be the first example in which microarrays are brought into clinical practice; it will allow identification of the large minority of patients who will benefit from chemotherapy following radiation or surgery, avoiding the current problem that some patients who do not actually need them are given drugs with unpleasant side-effects.

Beyond the single cell Cell-cell communication

Fiona Watt (Cancer Research UK, London, UK) spoke on the role of the integrin extracellular-matrix receptors in the formation and development of epithelial cancers called squamous cell carcinomas. She explained that integrins normally regulate epithelial differentiation by sending a 'do not differentiate' message to the cell; this signal can become subverted in tumors. She also described how an integrin that is frequently upregulated in squamous cell carcinomas helps cells to evade apoptosis. Finally she told us that aberrant integrin expression in the differentiated layers of the epidermis can exert a positive or negative influence on tumor formation in undifferentiated cells that have mutations in Ras.

Initiation, growth and invasion

Whereas Watt is asking about the steps to cancer formation in individual cells, Doug Hanahan (University of California, San Francisco, USA) asked why cancer cells seem to remain loyal to their organ of origin. In an incredibly elegant approach, Hanahan uses specific promoters to drive the expression of oncogenes such as SV40 T antigen in individual cells, such as those of pancreatic islets, in transgenic mice. One crucial finding has been that abrogation of the tumor suppressors p53 and Rb by tissue-specific expression of SV40 T antigen is not sufficient to cause tumor formation in the majority of cells. This is the first experiment in which it has been possible to follow the formation of a cancer from the beginning (or at least from the loss of two tumor suppressors).

Hanahan also addressed the last stage in cancer development and the one that has the most effect on the patient: progression to the invasive phenotype. Building on work from G. Christofori (Institute of Molecular Pathology, Vienna, Austria) showing that decreased expression of the cell-adhesion molecule E-cadherin correlates with carcinogenesis, Hanahan asked whether extracellular-matrix-associated proteases, which also affect cell adhesion, have a role in cancer progression. Although it appears that the protease MMP-9 is required for angiogenesis (as it activates the vascular endothelial growth factor, VEGF), the surprising observation is that neither MMP-9 nor the related protease MMP-2 is required for invasion of tissues by cancer cells. In a search for candidate molecules that may have a role in invasion, Hanahan considered IGF-2, levels of which increase during tumorigenesis. Loss of IGF-2 does not inhibit tumor growth but leads to tumors that are benign and well-defined. In contrast, overexpression of the receptor for IGF-2 (IGF-R1) gives rise to accelerated and wildly aggressive tumor formation - and E-cadherin expression is downregulated, as expected. Hanahan is now applying these very flexible models to build molecular profiles of the various stages of tumorigenesis using Affymetrix oligonucleotide microarrays. One interesting observation in the light of the expected role of proteases in invasion is that, of the genes whose expression is low in normal cells but high in tumors, the cathepsin family of cysteine/aspartic acid proteases stands out. Hanahan has therefore developed cathepsin inhibitors that he has used in stage-specific 'therapeutic trials' in his mouse models. The compounds show activity at all stages and appear to be able not only to exert an effect on cell proliferation (perhaps by affecting angiogenesis) but also to exert a strong effect on invasiveness. Hanahan has found that inflammatory cell types (expressing the antigens Mac1 and GR1) normally express high levels of cathepsins, which has led to the question, as yet unanswered, of what contribution inflammatory cells may make in the progression to invasiveness.

From cancer genes to cancer drugs

Paddy Johnston (Queens University, Belfast, UK) discussed cancer chemotherapy and the best strategies for cancer treatment. Thymidylate synthase (TS) has been a target of cancer drugs such as fluoropyrimidines and folate analogs for the last 40 years. Drug resistance in patients is often due to the upregulation of TS itself. Because p53 is frequently mutated in cancer cells, Johnston investigated whether the p53 pathway interacts with TS, using a tetracycline-regulated TS gene expressed in cells expressing or lacking wild-type p53. His results indicate that both TS levels and p53 status serve as good predictors of a cell's response to chemotherapy. On the strength of this, Johnston has used Affymetrix microarrays to seek genes whose expression changes following treatment with 5-fluoro-uracil, a fluoropyrimidine drug. He then asked whether inhibition of the cell death pathway that

is induced by the immune regulator Fas ligand contributes to resistance to TS inhibitors, and generated some very provocative results suggesting that sensitivity and acquired resistance to TS is very likely to depend upon p53 status and on regulation of more than one cell death pathway.

Many genes, many targets: one drug

The opening statement by Paul Workman (Institute for Cancer Research, Sutton, UK), a champion of translational cancer research, was that when it comes to cancer therapies, we can never know enough. If you think you have a good idea, you just need confidence in the target and to keep on trying until you can test the hypothesis in the ultimate model - the cancer patient. In his vision of modern cancer medicine, the identification of cancer genes will allow us to use diagnostic microarrays to define a patient's cancer, prognostic arrays to define the appropriate therapy, and bioinformatics to analyze the readouts from clinical trials and therapeutic regimens on individual patients. These same technologies will also be applied to the discovery of new therapeutic agents, although the ultimate goal would be an individualized strategy for cancer prevention. With regard to cancer drug discovery, the key issues that Workman considered were whether the cancer is due to a hard-wired dependency on an oncogene that opens a therapeutic window between healthy and cancer cells; whether correction of a single defect will be sufficient for a cure; whether drug resistance is likely to be acquired; and finally whether the inhibition of several pathways will be required.

Consideration of these questions led Workman to choose Hsp90 as a target. Hsp90 is frequently over-expressed in human cancers and is required for the folding of proteins such as Erb-B2, the kinases Raf, CDK4 and Polo-1, mutant p53, the receptor tyrosine kinase Met, human telomerase reverse transcriptase and nuclear hormone receptors. Between them, these proteins cover each of the deleterious events that were called the 'hallmarks of cancer' by Hanahan and R.A. Weinberg in 2000. Loss of Hsp90 function is likely to lead to the degradation of Hsp90 targets, causing cell-cycle arrest and/or apoptosis of the cancer cells whose survival depended on the targets. Despite many of the problems often associated with drug development - and the additional problems associated with sceptical colleagues - Workman has been able to validate Hsp90 as a drug target and initiate clinical trials of two Hsp90 inhibitors, 17AAG and geldanamycin.

One multi-protein family, many specific drugs?

The work of Louise Johnson (University of Oxford, UK) is driven by the idea that the cyclin-dependent protein kinases (CDKs) are in fact excellent candidate drug targets (contrary to Tim Hunt's opinion, mentioned above). This rationale is justified by the elegant work of Johnson and others who are dissecting, at the atomic level, exactly how specificity is built into these basic cellular timekeepers. Using structural information, it has been possible to design inhibitors that, at least

in vitro, show a more than 100-fold preference for Cdk2 and Cdk1 over Cdk4. Given the clinical experience with Gleevec, a kinase inhibitor and the first drug to be identified using rational approaches to drug design, such a range of potency may be sufficient for clinical applications. Although it still remains to be demonstrated that targeting Cdk1 and/or Cdk2 is a desirable clinical goal, this work is at least leading us to the tools we need to be able to do the experiment.

Johnson moved away from inhibitors of the protein-kinase activity of Cdk2 to discuss the structural basis for the recognition and binding of substrates by cyclins, the regulatory subunits of CDKs. Her group are currently building on published data to model the interactions of the cyclin-A-Cdk2 complex with peptides derived from a range of its substrates. The hope is that these studies will lead to a new way of inhibiting CDKs in which the phosphorylation of only one tumor-specific substrate will be inhibited.

One cancer pathway targeted by drugs at many levels

David Lane (Cyclacel and University of Dundee, UK) followed a similar theme, starting from a molecular understanding of p53 and proceeding via structural biology to the *in silico* identification and engineering of small-molecule inhibitors of Mdm2, a ubiquitin ligase that targets p53 for degradation. The idea is that cells in which p53 is stable will be driven into apoptosis, a process that is frequently defective in cancer cells. The advantage of focusing on the p53 pathway, from Lane's perspective, is that there are many points at which one can intervene: inhibitors of the proteasome or of Mdm2, or mimics of ARF (an inhibitor of Mdm2) should all have the same effect: stabilizing wild-type p53, allowing it to kill tumorigenic cells. One strategy that holds great hope, yet has still to meet expectations, is the inhibition of nuclear export: so far, leptomycin B is the only potential drug that gives rise to the transcriptionally active form of p53 that will kill cells. The therapies that can activate p53 without inducing DNA damage will work only in the half of human tumors that retain wild-type p53; other approaches, such as the CDK inhibitors his group are also developing, will be needed in cells lacking p53.

Many drugs to regulate one protein

Bill Kaelin (Dana-Farber Cancer Institute, Boston, USA) started by giving the background to the genetic von-Hippel-Lindau (VHL) disease that includes a predisposition to cancer. One peculiarity of this disease is that although it is recessive, meaning that both alleles of the *VHL* disease gene need to be mutated for the disease to manifest itself, 90% of cells in which the first allele is inactivated rapidly lose the second allele. The *VHL* gene encodes an E3 ubiquitin ligase, one of the major substrates of which is the normally labile α subunit of a transcription factor called hypoxia-inducible factor (HIF α). In cells lacking functional VHL, HIF α accumulates, leading to the increased production of blood vessels and red blood cells that are hallmarks of VHL disease. These

processes would usually be regulated by oxygen levels: a proline residue of HIF α is hydroxylated in response to oxygen, leading to the recruitment of VHL and degradation of HIF α . Kaelin's group set out to purify the HIF α hydroxylase by traditional methods, but in the meantime the group of Eugene Koonin (National Center for Biotechnology Information, National Institutes of Health, Bethesda, USA) identified EglN-C *in silico* as a candidate proline hydroxylase. There are two human EglN-C homologs and one nematode homolog, and Kaelin used small inhibitory RNAs (siRNAs) to show that loss of only one of the human homologs, EglN-1, resulted in stabilization of HIF α . Kaelin then looked at the interplay between HIF α and VHL in cancer formation. Downregulation of HIF α using siRNAs prevented tumor formation, indicating that stabilization of HIF α may be necessary for tumor formation. In addition, stabilization of HIF α by mutation of its hydroxylated proline to alanine allowed cells to acquire a cancerous phenotype even in the presence of wild-type VHL protein, suggesting that stable HIF α may be sufficient to drive tumor formation. Kaelin's group has already shown that inhibitors of some of the proteins whose expression is upregulated by HIF α , such as VEGF, have beneficial clinical effects in cancers such as metastatic renal carcinoma. Starting from a genetically simple disease, this work clearly shows that there may be many ways to prevent tumor growth.

In summary, this is a time of great hope in cancer research, given the discovery of Gleevec, the first clinically successful, rationally identified drug, and now that microarray technologies are allowing us to identify new pathways and to find the right therapies for each patient. But rational drug design still has some way to go: Gleevec was really identified using only semi-rational methods (the target was chosen, but the screen was still a random walk through ATP analogs). Similarly, microarrays have only scratched the surface of molecular characterization of cancers, and we are just beginning to get a feel for their applications in diagnosis and prognosis. Tools are needed that will allow us to determine whether a new protein that is implicated at some stage in cancer really is a good drug target. The Hutchison/MRC Centre and other institutes are responding to some of these needs. From the very high standard of this symposium, the future of translational cancer research seems bright.

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