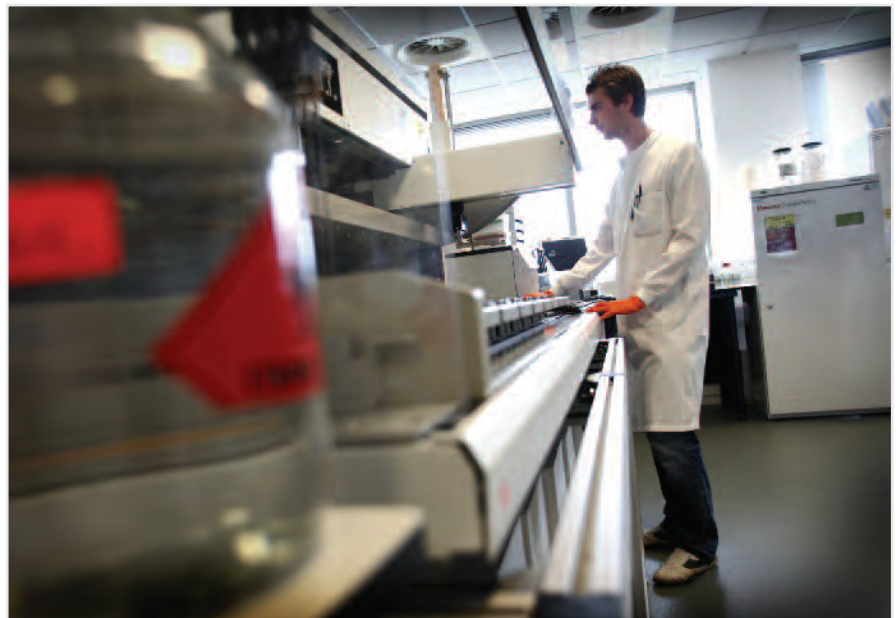


The Cancer genetics and genomics programme investigates somatically acquired alterations in cancer genomes in order to identify those genes that contribute to cancer development, elucidate mutational processes operative in these genomes, organise and present this information publicly, use it to understand responsiveness to anti-cancer therapies and improve patient management.

- Cancer Genome Project
- Cancer genome profiling
- Cancer Translation Project



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Scientist working in the Cancer Genome Project laboratory. High-throughput approaches are utilised to fully elucidate the genes important in a variety of cancers.

Over the past year, the Cancer Genome Project has been pursuing several lines of study to characterise the somatically acquired genetic events underlying a range of cancers. Analyses of large datasets have revealed the signatures of mutation from cigarette smoke and UV radiation, while next-generation sequencing technologies have begun to uncover fully the genomic complexity of breast cancer. Delineating patterns of genomic losses and gains in rearranged genomes has suggested which mutations are likely to be drivers and which passengers. Detailed characterisation of individual cancer genomes is also raising the possibility of patient-specific markers for clinically monitoring response to therapy in patients with solid tumours.

Work on renal cancer has identified mutations in several histone-modifying enzymes, emphasising the likely importance of chromatin modification in cancer development. As with breast cancer, research on renal cancer is revealing a great diversity of genetic changes even within a single type of tumour.

This year also saw the first public release of data from the genomics of treatment response project – a collaboration between the Sanger Institute and Massachusetts General Hospital. This large-scale screen aims to identify genetic signatures of responsiveness to anti-tumour agents.

Future directions

With the increasing pace of sequencing technology development, the move to whole-genome shotgun sequencing as the primary means of characterising cancer genomes is imminent. The Cancer Genome Project will expand substantially on its efforts in breast cancer, leading an international working group with the aim of sequencing more than 1500 breast cancer genomes over the coming few years. In addition, major initiatives in bone cancer and myelodysplastic syndrome will be undertaken. These three areas of work are part of the International Cancer Genome Consortium, which aims to characterise in depth more than 25 000 cancer genomes from all major cancer types within the next five to seven years.

Faculty members

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The uniqueness of cancer

Cancer genomes are turning out to be surprisingly complex – indeed, each patient may have a genetically unique cancer.

It has long been recognised that cancer is not a single disease but many. Even cancer of a single organ type can take several forms. Genomic approaches have pushed this differentiation still further, revealing that even histologically similar tumours may have quite distinct underlying genetic defects. Recent work on breast cancer has revealed a sobering degree of variation, but individualisation may create opportunities for improved clinical management.

As in so many other areas, next-generation sequencing offers many new opportunities in cancer genomics. One important application is the characterisation of rearrangements in cancers – known to be important in blood cancers but whose significance in solid tumours has been less clear.

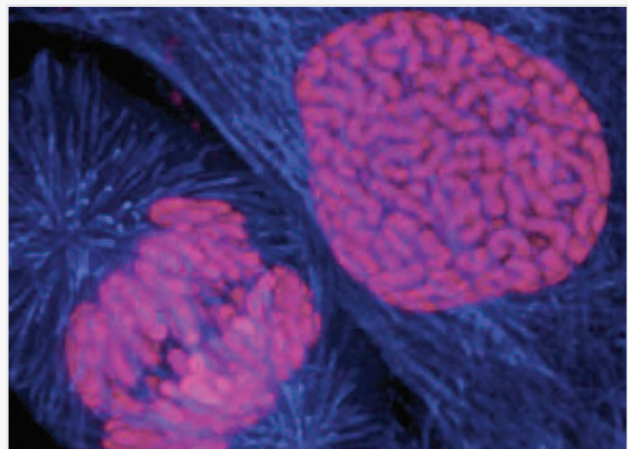
An analysis of 24 breast cancers by the Cancer Genome Project revealed a great diversity of rearrangements. The genome of some tumours was scarcely disturbed, while others were scarred by hundreds of rearrangements.

Future work will also involve continued development of the COSMIC database as the principal public resource for cataloguing and presenting somatic mutations in cancer. In addition, there are plans to expand efforts to study cancers arising in genetically engineered mouse models and in transposon-based screens to fully exploit comparative oncogenomics as a tool to further understand human cancer. The results of all of these efforts will be fed into the large-scale translation project to empower the analyses of genomic determinants of response to anti-cancer agents in a large variety of human cancers.

Although the complexity is daunting, there are some chinks of light. Characteristic patterns could be seen among the genetic chaos, often related to the presence of particular mutated cancer genes – suggesting that it may be possible to develop genetically based categorisation systems. It is also possible that certain rearrangement patterns may be associated with sensitivity to particular treatments.

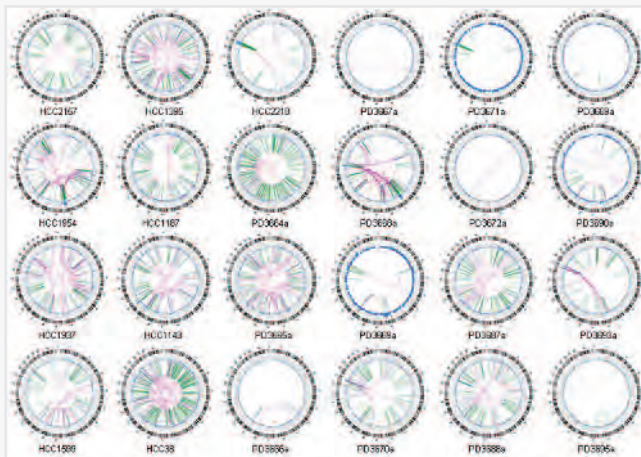
Further work has highlighted an additional possible benefit. Next-generation sequencing was able to identify patient-specific rearrangements in three cancer types, and DNA-based tests could detect such rearrangements in blood samples with exquisite sensitivity. Potentially, this could provide a simple way to monitor a patient's disease status and response to treatment over time, and reveal any early signs of relapse.

Stephens PJ et al. Complex landscapes of somatic rearrangement in human breast cancer genomes. *Nature*. 2009;462(7276):1005-10. PMID: 20033038.
McBride DJ et al. Use of cancer-specific genomic rearrangements to quantify disease burden in plasma from patients with solid tumors. *Genes Chromosomes Cancer*. 2010 Nov;49(11):1062-9. PMID: 20725990.



Human breast cancer cells dividing. An analysis of 24 breast cancers by the Cancer Genome Project revealed a great diversity of rearrangements.

The Cancer Genome Project aims to characterise somatic mutations in human cancer in order to identify new cancer genes and improve understanding of how cancer develops.



Stephens PJ et al. *Nature* 2009; 462(7276):1005-10.
doi:10.1038/nature08645

Genome-wide plots of somatic rearrangements in all 24 breast cancers in the study. Each circle represents the 23 human chromosomes and the arcs depict genomic rearrangements within and between chromosomes.

Through large-scale cancer genomics, we aim to discover new mutated cancer genes, with the ultimate aim of improving diagnosis and treatment of cancer. Further, we aim to understand underlying patterns of somatic mutations, which reflect the mutational processes and environmental exposures that have influenced the evolution of each cancer.

Over the past decade we have conducted increasingly extensive systematic sequencing screens of cancer genomes. In the past year we generated genome-wide sequences of two cancers – a malignant melanoma and a small-cell lung cancer – yielding the first two complete catalogues of somatic mutations in cancer. These mutation catalogues bore the imprints of ultraviolet light and tobacco carcinogen exposure, which have been implicated in melanoma and lung cancer, respectively, and provided remarkable insights into the evolution of each cancer.

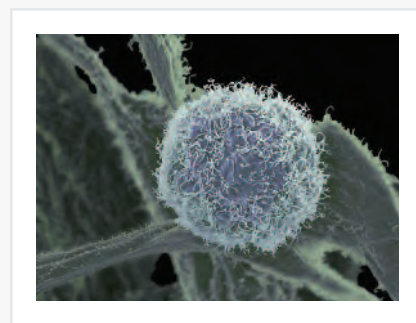
We have also carried out extensive sequencing for mutations in protein-coding exons of more than 100 kidney cancers. These studies led to the discovery of multiple new cancer genes and highlighted the role of mutations affecting the chromatin-modifying and remodelling machinery in human cancer.

There is strong clinical evidence that responsiveness of cancers to some anticancer drugs is determined by the presence of mutations in certain cancer genes. To extend our knowledge of the relationship between

mutated cancer genes and drug responsiveness, we are exposing 1000 genomically characterised human cancer cell lines to 400 anticancer drugs as part of the Cancer Translation Project (<http://www.sanger.ac.uk/genetics/CGP/translation/>).

We continue to maintain and develop the COSMIC (Catalogue of Somatic Mutations in Cancer) database, in which we aim to record all somatic mutations ever reported in cancer. COSMIC is the only comprehensive database of this type worldwide.

Finally, we continue to provide central leadership in the International Cancer Genome Consortium, a worldwide collaboration aiming to generate genome sequences of more than 25 000 human cancers over the next 5–10 years.



Scanning electron micrograph of a human melanoma cell. UV light creates distinct signatures of DNA damage in the genome, identifiable by DNA sequencing.

Anne Weston, LRI, CRUK, Wellcome Images



Wellcome Library, London



Wellcome Library, London

➤ **An analysis of genomic copy number changes in more than 700 cancers, and how to distinguish between driver (cancer-causing) and passenger mutations.**

Bignell GR et al. Signatures of mutation and selection in the cancer genome. *Nature* 2010; 463:893–8.

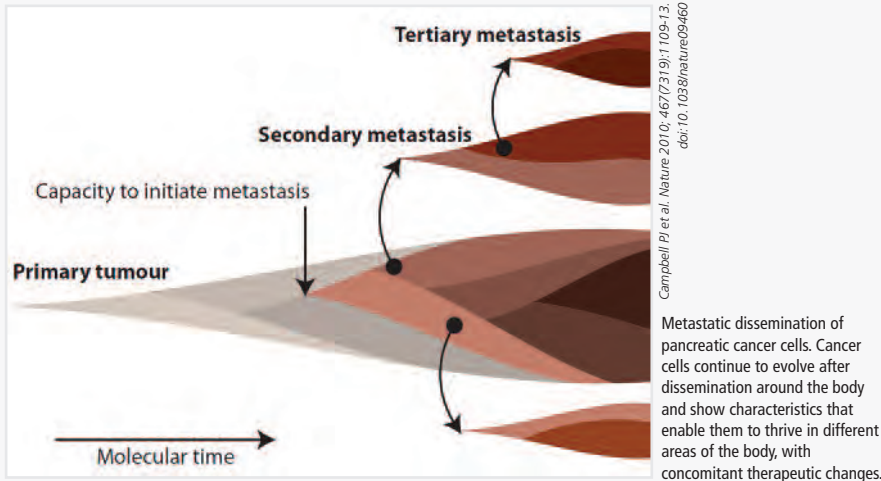
➤ **Sequencing of 100 kidney cancers yields several new cancer genes and highlights the role of mutations in the chromatin-modelling machinery.**

Dalglish GL et al. Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes. *Nature* 2010; 463:360–3.

➤ **The full set of somatic mutations in a malignant melanoma reveals the imprint of damage from ultraviolet light and other mutagenic and DNA repair processes.**

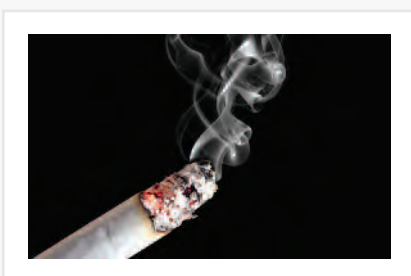
Pleasance ED et al. A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature* 2010; 463:191–6.

We aim to generate genome-wide catalogues of mutations acquired by a cancer during its development, to shed light on the biological processes underpinning cancer and the clinical consequences of specific genetic changes.



High-throughput DNA sequencing technology now allows us to document the accumulation of genetic changes, opening up an unprecedented vista of the forces shaping our genome. We can compare the genetic variants found in malignant cells with those found in normal cells from that same individual, allowing us to identify all the mutations acquired by the cancer clone during its evolution. Among these mutations lurk those responsible for the cancer's malignant behaviour.

We have shown that genome-wide compendia of somatic mutations can be generated from next-generation sequencing data, providing fascinating insight into cancer development. We can see, in exquisite detail, the ravaged cancer genome displaying the scars of mutational forces deriving from both environmental exposures, such as tobacco smoking, and DNA repair defects.



In a lung cancer, the clone of cells that ultimately becomes cancerous acquires, over its lifetime, an average of one mutation for every 15 cigarettes smoked.

We have recently completed an analysis of metastatic pancreatic cancer, which has shone light on the dynamics of tumour spread to distant sites. We identified genomic rearrangements in 13 patients with pancreatic cancer and looked for these rearrangements in other metastases from each individual. Intriguingly, cancer cells continue to evolve, sometimes quite extensively, after dissemination around the body. Thus metastases are not genetically identical, and may ultimately show phenotypic and therapeutic differences.

The potential for mapping mutations in patients in a clinically relevant timeframe opens up substantial translational opportunities. We have been pursuing the possibility that tumour-specific genomic rearrangements can be used as a genetic fingerprint for a cancer. In three patients, we have shown that specific rearrangements can be sensitively detected in blood samples. In serial blood samples, levels of tumour burden over time and on treatment strongly correlated with clinical status.

The major challenge now is to take the preliminary data from a handful of cancers, and expand it to hundreds or thousands of cases. This will require collaboration across disciplines, with clinicians, biologists, geneticists and informaticians all playing key roles. These collaborations have been formalised under the auspices of the International Cancer Genome Consortium.



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A genome-wide catalogue of somatic mutations in a small cell lung cancer cell line.

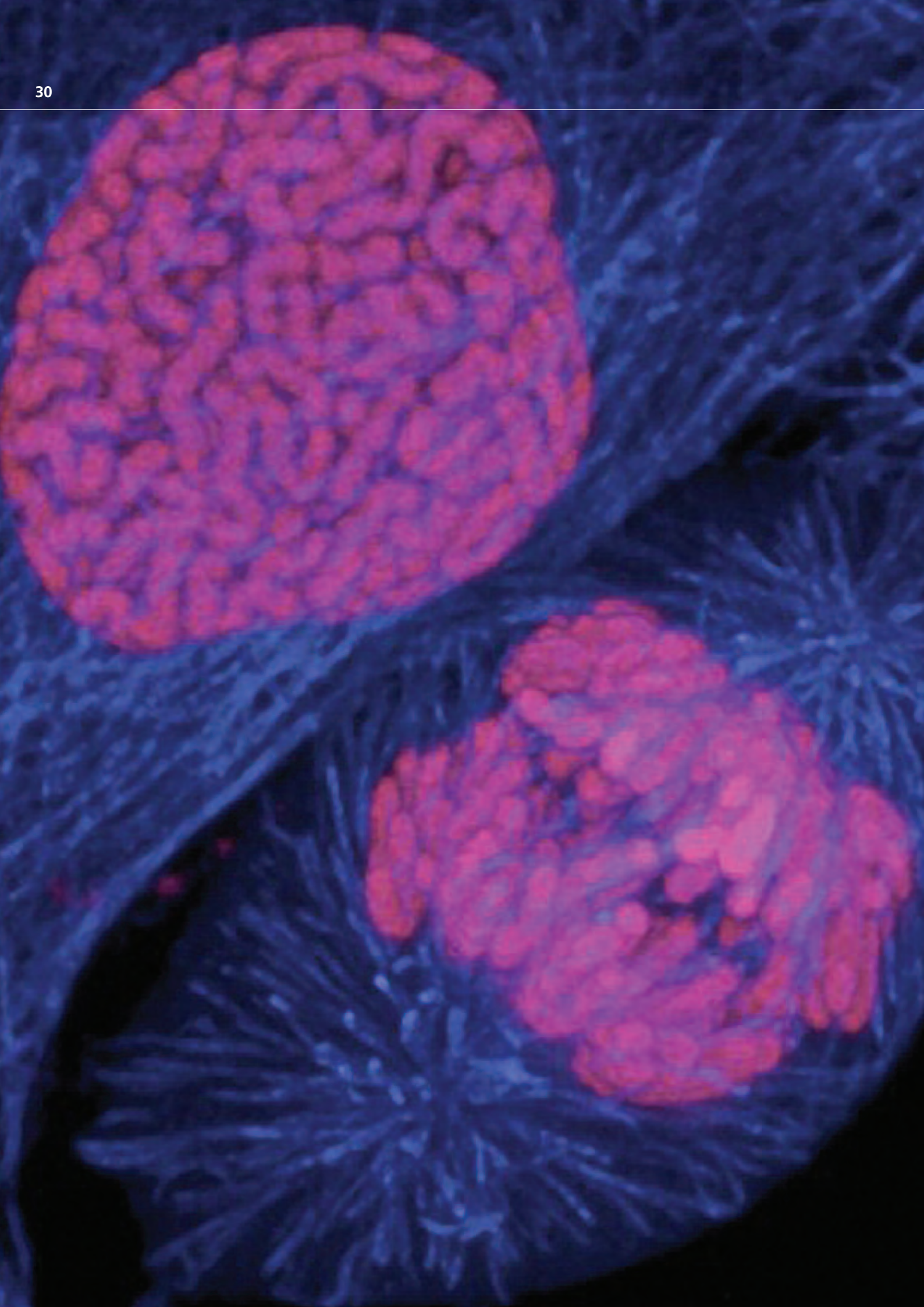
Pleasance ED et al. A small cell lung cancer genome with complex signatures of tobacco exposure. *Nature* 2010; 463(7278):184-90.

Cancer-specific rearrangements can be used as a genetic fingerprint of a cancer in an individual, allowing disease burden to be quantified in real time.

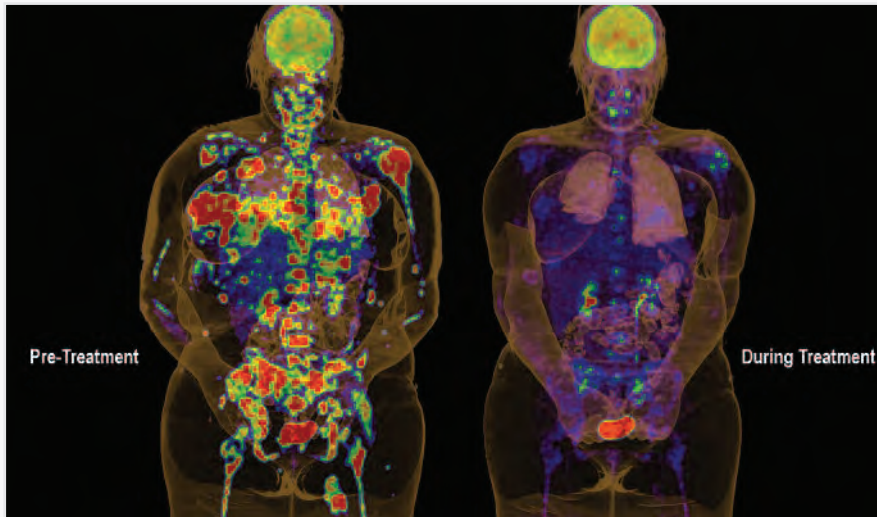
McBride DJ et al. Use of cancer-specific genomic rearrangements to quantify disease burden in plasma from patients with solid tumors. *Genes Chromosomes Cancer* 2010 Nov;49(11):1062-9.

Tracking the evolution of genomic rearrangements in 13 patients with metastatic pancreatic cancer, as metastases adapt to different organs.

Campbell PJ et al. The patterns and dynamics of genomic instability in metastatic pancreatic cancer. *Nature* 2010; 467(7319):1109-13.



The Cancer Translation Project aims to screen 400 therapeutic agents against 1000 cancer cell lines, to identify genetic biomarkers that can be used to distinguish subsets of patients most likely to respond to targeted therapies.



Grant McArthur, the Peter MacCallum Cancer Centre, Australia

Dramatic response to treatment with the *BRAF* inhibitor PLX4032 seen in a melanoma patient whose tumour harbours the V600E *BRAF* mutation. PET scans were taken at baseline and 15 days later.

Cancer treatments are increasingly 'rationally' based – targeted at specific cellular abnormalities linked to underlying genetic mutations. Because cancers are so genetically heterogeneous, however, there is rarely a simple relationship between a cancer type and its response to new therapeutic agents. Moreover, different types of cancer may share mutations in the same gene and therefore might be expected to respond to the same drug.

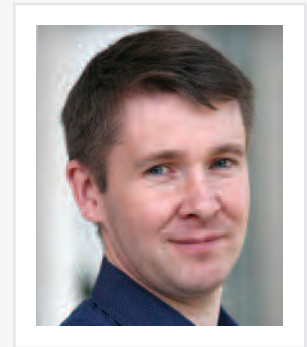
Systematic sequencing of large numbers of clinical tumour samples using next-generation sequencing will, over the next 2–3 years, generate large quantities of data describing the genomic architecture of many types of cancer. Our success in translating these catalogues of somatic mutations into clinically relevant information will depend, in part, on understanding their implications for treatment.

To achieve this, we need a better understanding of how genetically well-characterised cancers respond to targeted therapeutic agents. Empirically, this can be achieved by screening agents against a wide range of cancers with defined genetic backgrounds, so statistically significant correlations can be identified between a specific genetic change (or combination of changes) and sensitivity to a given drug.

To this end, the Cancer Translation Project, a collaboration between the Cancer Genome Project at the Sanger Institute and the Center for Molecular Therapeutics, Massachusetts General Hospital Cancer Center, USA, is screening 400 preclinical and clinical therapeutic agents against 1000 genetically well-characterised human cancer cell lines.

Data are being made freely available through the Cancer Genome Project website. The first dataset was released in July 2010 and information will be updated every 3–4 months.

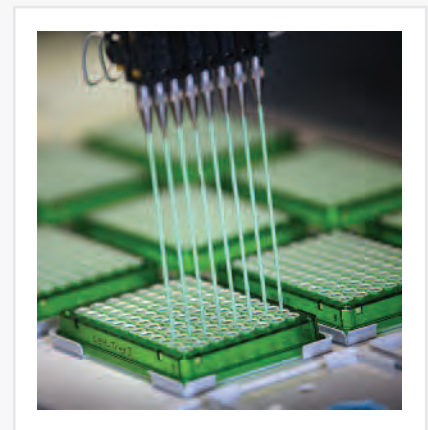
These data are likely to be of great value to both the clinical and scientific communities. Clinically, the data will provide a way to match the right drug with the right genetic context, to identify the cancer drug a patient is most likely to respond to. Scientifically, the data will provide insight into the biochemistry of cancer cells, and suggest ways to improve drug development.



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Collaborating Faculty

Andy Futreal
Mike Stratton



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We are screening 400 preclinical and clinical drugs against 1000 genetically well-characterised human cancer cell lines, in collaboration with the Center for Molecular Therapeutics, Massachusetts General Hospital Cancer Center, USA.