Advances in molecular targets and cancer therapeutics

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The annual *Molecular Targets and Cancer Therapeutics* (17–21 November 2003, Boston, MA, USA) symposium is the foremost meeting in the cancer field that focuses specifically on cancer-associated molecular targets and their exploitation in the discovery and development of selective cancer therapeutic agents[i].

Crucial issues

The conference programme attempted to address the following crucial issues in cancer therapeutic research: the use of

genomic and proteomic technologies in relation to target identification and validation, target selection for therapeutic intervention, lead identification and drug development strategies, molecular profiling and biomarkers in the clinic and the barriers to clinical testing of targeted agents.

Genomic and proteomic technologies

The Human Genome Project has undoubtedly transformed our view on the practice of cancer biology and has provided a huge impetus towards elucidation of new potential targets to be exploited for the treatment of cancer. For example, global analysis (e.g. all mRNAs or all proteins) for a particular system is now possible. In many ways, the Human Genome Project has stimulated a paradigm shift in research because the gathering and presentation of information has become equally important, which has influenced the perception of biology as an information science dissociated from classical hypothesis-based research.

The novel concept of systems biology (the way in which information evolves to explain the emergent properties of a system) was beautifully illustrated in a keynote presentation by Leroy Hood (University of Washington; http://www.washington.edu). Other presentations by Geoffrey Duyk (Exelixis; http://www.exelixis.com) and Todd Golub (Dana-Farber Cancer Institute; http://www.dfci.harvard.edu) on genomics and Michael Moran (MDS Proteomics; http://www.mdsp.com) on phosphoproteomics described the tremendous progress and huge potential of these fields for transforming our understanding of signalling and regulatory pathways in cancer cells. Gregory Hannon (Cold Spring Harbor Laboratory; http://www.cshl.org) discussed the burgeoning field of RNAi in the elucidation of biochemical mechanisms.

Target selection

A conference debate on the subject of target selection produced some lively exchanges between the panellists and, although there was broad agreement on certain issues including target 'drugability' and the need for more clinically relevant mouse tumour models, there were also areas of contention, for example, the issue of how much detailed knowledge of the drug target and pharmacological mechanism is required before taking a new agent forward into the clinic.

Following the clinical success of the Novartis Bcr–Abl tyrosine kinase inhibitor STI571 (Gleevec™, also known as Glivec™; imatinib mesylate; http://www.novartis.com) in the treatment of chronic myeloid leukaemia (CML) and other emerging indications, the inhibition of alternative kinase targets in the clinic was the subject of a plenary session this year. Judith Sebolt-Leopold (Pfizer; http://www.pfizer.com/main.html) described the identification of highly specific mitogen-activated protein kinase kinase (MEK) inhibitors that resulted in the development of PD0325901 as a clinical trial candidate. Richard Marais (Institute of Cancer Research; http://www.icr.ac.uk) described the role of the serine/threonine-protein kinase B-RAF as an important therapeutic target in human cancer (mutated in ~7% of cancers, most notably in melanoma), and Donald Small (John Hopkins University School of Medicine; http://www.hopkinsmedicine.org/som/index.html) discussed FLT-3, a tyrosine kinase receptor prevalent in acute myeloid leukaemia (AML). The discovery of a potent anilinoquinazoline inhibitor of Aurora kinase, a serine/threonine kinase family that has recently been shown to play a crucial role in coordinating cell progression through mitosis, was presented by Nick Keen (AstraZeneca; http://www.astrazeneca.com).

Drug discovery

The requirement for lead compounds with properties suitable for further development against emerging anticancer drug targets as yet unexplored in the clinic remains a major obstacle to clinical progress, particularly in the most common solid tumour types. A range of strategies, from structure-based drug design to high-throughput screening of large compound libraries, have been employed to address this central question in drug discovery. Further progress in this field was reported at the meeting.

A keynote lecture delivered by Alex Matter (Novartis Pharma AG; http://www.novartis.com) illustrated some of the difficulties underlying the often (painfully) slow progress in cancer drug discovery and development. The reasons presented to explain the problems encountered included, conceptual uncertainties related to target selection, the complexity of the drug design process and lead identification, lack of predictive quality of current cellular and animal models, and lack of reliable clinical biomarker technologies. Several clinically used kinase inhibitors developed by Novartis (e.g. the staurosporine derivative PKC412 used in the treatment of AML) were presented to illustrate the drug discovery process.

The high-throughput potency-based screening process typically used for mining compound libraries against a protein target of interest is limited in that only a small fraction of the theoretical number of small, drug-like molecules can be evaluated. A workshop dedicated to structure-based drug discovery illustrated some of the cutting-edge technologies currently used in the search for lead molecules in cancer drug discovery. For example, Michael Milburn (Plexxikon; http://www.plexxikon.com) illustrated the efficient use of X-ray

crystallography-based techniques that incorporate the Plexxikon scaffold-based drug discovery platform. In addition, Harren Jhoti (Astex Technology; http://www.astex-technology.com/index.html) described Pyramid™ fragment library technology. The concepts of chemical genetics and diversity-orientated synthesis (leading to libraries of molecules with high skeletal and stereochemical diversity) were described by Stuart Schreiber (Harvard University; http://www.harvard.edu).

Kinase inhibitors in the clinic: Gleevec™

Gleevec™ remains the most remarkable breakthrough in the field of small molecules 'targeted' against cancer in recent years, which was initially used in the treatment of chronic myeloid leukaemia (CML), and more recently in the therapy of other tumour types [e.g. gastrointestinal stromal tumour (GIST)]. The success of Gleevec™ in CML is easy to understand given the fundamental genetic mutation that is the basis for the development and progression of disease. The majority of patients suffering from CML express the Bcr–Abl fusion protein tyrosine kinase, and it is this fusion protein that effects disease progression. Therefore, Bcr–Abl represents an ideal target for therapeutic intervention. Our understanding of CML at the molecular level has advanced tremendously, indicating the way forward for cancer drug discovery and development. John Kuriyan (University of California, Berkeley; http://www.berkeley.edu) discussed the structural analysis of the regulation of c-Abl and Gleevec™ specificity. The elucidation of the multiple Bcr–Abl kinase domain mutations that confer resistance to Gleevec™, particularly in advanced stages of CML, were presented by Charles Sawyers (University of California, Los Angeles; http://www.ucla.edu). The implications of these findings for the design of second generation versions of Gleevec™ that overcome common resistance mechanisms, thus enhancing the prospects for the effective treatment of Gleevec™-resistant patients, were also discussed.

The next Gleevec™?

Unfortunately, in solid forms of human cancer, the disease is more complex than CML because the cancerous phenotype is usually maintained by several deregulated pathways. To see real advances in clinical efficacy against solid tumours, several targeted therapeutic agents will have to be developed and used in synergistic combinations (tailored to tumour profiles of individual patients). Alternatively, the development of novel agents that 'hit' several relevant targets simultaneously, or hit a target that has a central role in a range of cancer-associated signalling pathways, could provide the long sought-after advances in the treatment of the most commonly occurring solid tumours. Given the huge advances that have been made in recent years in our understanding of cancer cell biology at the individual tumour level, this is an attainable goal, but one that will probably take a few more years to realise.

Barriers to clinical testing of targeted agents

A hotly debated topic was the extent to which pharmacodynamic endpoints should, or could, be integrated into clinical trials of targeted novel agents as biomarkers for patient selection or treatment efficacy. The barriers to clinical testing of targeted agents discussed included the la ck of data on new cancer targets at clinical trial onset, and the lack of data on host and tumour genetic heterogeneity. The complexities involved in selection of drug combinations in the clinic were also debated. However, there was a broad consensus concerning the positive effects of the increasing use of relevant pharmacodynamic endpoints to guide patient selection and clinical response in future trials.

Conclusions

The remarkable advances in our understanding of signalling and regulatory pathways in cancer cells, fuelled by advances in genomic and proteomic technologies, provide tremendous optimism for diagnosis and treatment of the disease in the near future. This wealth of data provide a host of potential new cancer-relevant targets. Despite the rapid advances in combinatorial chemistry and high-throughput screening technologies, transforming new target data into lead compounds with clinical potential, even where knowledge of the target structure is well defined, remains a bottleneck in the discovery process. Alternative structure-based strategies to discover novel lead compounds are likely to continue to develop.

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[i]The organising bodies, the American Association for Cancer Research (AACR), US National Cancer Institute (NCI) and European Organisation for the Research and Treatment of Cancer (EORTC), represent the largest professional bodies in this field in the USA and Europe. The conference abstracts are published as a Supplement to *Clinical Cancer Research*, Volume 9, Number 16.