and computer science departments at MIT, and graduates are rigorously selected on the basis of their ability to interface between disciplines. Other efforts such as those at Princeton and Harvard were also outlined, although a key point that was made was whether such integrated approaches need to be taught much earlier than the undergraduate and graduate levels. Another important point raised was that these efforts are designed very much for the future of the field whereas success stories are needed now, otherwise the field will lose momentum, particularly as far as the pharmaceutical industry is concerned. Tadmor emphasized that it was important to have industry involved and that for the field to move forward it is necessary to have researchers in both academic and industrial arenas that see value in the approach, although she conceded that the pharmaceutical industry was the most conservative industry that MIT has ever collaborated with.

The final exchange session was chaired in authoritative fashion by Bernard Palsson (University of California San Diego; http://www.ucsd.edu) and served to provide a summary and overview of the meeting, identifying crucial issues in systems biology, including mathematical method development and integration of multiple high-throughput datasets.

The conference closed with a session on the leading consortium programs aiming to help speed the adoption of systems biology methodologies. These included presentations by Eric Neumann (Aventis; http://www.aventis.com) on the Semantic Web, Joanne Luciano (Harvard Medical School) on the BioPAX initiative and Randall Julian (Eli Lilly; http://www.lilly.com) discussing the HUPO Proteomic Standards Initiative.

Concluding remarks

The Implementing Systems Biology meeting was interesting and made a pleasant change to the standard conference format. This is clearly a subject that needs active dialogue within the community and this meeting, with its scientific exchange sessions, encouraged such debate. It is clear that there are many other issues within the drug discovery arena that could benefit from being discussed in a similar matter. The meeting was attended by a relatively small number of delegates and it was disappointing that there was not a greater representation from large pharmaceutical companies but, despite this, the meeting was still useful and timely. Perhaps unsurprisingly, there were little answers forthcoming to some of the issues raised but the meeting still served to provide an excellent appreciation of the current status of the field. Clearly, industry is not going to wholeheartedly embrace systems biology straightaway. However, a selective and practical introduction of systems approaches in the discovery pipeline might be the way forward. There are certain applications of integrative approaches that might pay quick dividends, such as toxicogenomics, and in this way the value of systems biology will become obvious, providing the impetus for a greater adoption of this approach within industry.

Molecular targets and cancer therapeutics

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The *16th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics* was held 28 September to 1st October in Geneva, Switzerland. This annual meeting is the premier world conference devoted to the elucidation and validation of molecular targets in cancer and the discovery and development of cancer therapeutic strategies. The meeting is organised under the auspices of these leading cancer research societies: the European Organisation for Research and Treatment of cancer (EORTC); the US National Cancer Institute (NCI); and the American Association of Cancer Research (AACR)*.

The inclusion of parallel workshops covering contemporary topics such as 'Marketing Approval for Anticancer Agents', 'Preclinical Models', 'Mechanistic Combinations' and 'Pharmaceutical Industry, Investigators and Institutions: Partners or Tools?' was a particularly pleasing aspect of the meeting, and in the last case provoked some intense and passionate debate on the relationship between academic clinicians and 'big pharma', with notable contributions from Eric Rowinsky (Institute for Drug Development, San Antonio, Texas; http://www.ctrc.saci.org) and George Blackledge (AstraZeneca, UK; http://www.astrazeneca.co.uk).

The breadth of topics covered by the plenary presentations gives a snapshot and flavour of the most sought after

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targets and avenues for therapeutic exploitation relevant in the field today, including: proteomics/genomics; Akt/PTEN survival pathways; proteasome inhibitors and antichaperone drugs; hypoxia as a target (HIF-1); chromatin-modifying agents; targets for angiogenesis inhibition; apoptosis pathway-targeting agents; stroma/metastasis as a target and cancer chemopreventative agents.

Target selection and 'surprising' drug targets

There is no doubt that our understanding of cancer biology at the cellular level has progressed enormously during the past decade, fuelled by advances in areas such as proteomics and genomics. These advances inevitably result in the identification of a wealth of potential cancer drug targets, with varying degrees of 'validation' in the sense of their contribution to the development and progression of tumours. However, the slow progression of drug target knowledge into agents active in the clinic continues to frustrate cancer scientists for the following reasons.

First, selective single-agent therapy (targeted agents) against what was considered to be a good target has often proven ineffective in the clinic, necessitating combination strategies with traditional cytotoxic therapies, other targeted agents, or radiotherapy. An example of one such target discussed at the meeting is the vascular endothelial growth factor receptor (VEGF), which plays a central role in the angiogenesis process common to developing solid tumours. Conversely, the concept of opening up the tumour blood supply selectively in tumours through the use of an endothelin antagonist, in order to better facilitate delivery of cancer drugs or radiotherapy, was presented (Olivier Feron, University of Louvain Medical School, Brussels, Belgium; http://www.ucl.ac.be).

Second, the continuing emergence of useful agents in the clinic acting against targets which, purely on the basis of knowledge of contemporary cancer biology, would not be considered appropriate for therapeutic exploitation. Examples of such targets include the proteosome and the molecular chaperone Hsp90. The recently licensed proteosome inhibitor Velcade® (multiple myeloma) provides a relevant example of an agent acting against a 'surprising' molecular target.

Molecules to medicines or targets to treatment

The Michel Clavel lecture, delivered by Herbie Newell (University of Newcastle, UK; http://www.ncl.ac.uk) reflected on the drug development process, using case histories in cancer drug development to address the central question of the role and importance of target validation in cancer drug development. The case was made that for the established alkylating agents and antimetabolites, clinical activity was demonstrated before the targets were defined in any detail. Even the first wave of 'targeted' agents exemplified by imatinib (Gleevec®) have been found to hit a range of targets, despite being originally developed as selective agents.

The case of Eli Lilly's pemetrexed (Alimta®), granted regulatory approval this year for the treatment of non-small cell lung cancer and arguably this year's 'cancer drug of the year', was explored in further detail. Pemetrexed is a 'multitargeted' drug that simultaneously inhibits three separate targets long known to be relevant in antifolate drug development.

Targeted drugs or multitargeted ('dirty') drugs

Arguably the most important (and most often cited) 'targeted' agent to emerge in recent years has been the Novartis compound imatinib (Gleevec®), originally licensed in Chronic Myelogenous Leukaemia (CML) and targeting the essential fusion protein Bcr-Abl. Since this time data has emerged regarding the activity of imatinib in other tumour types including gastrointestinal stromal tumours (GIST), driven by the tyrosine kinase protein c-kit. Furthermore data has now been released detailing the clinical activity of imatinib against a rare malignant skin tumour known as dermatofibrosarcoma protuberans (DFSP), a disease reliant on a aberrant translocation product of another tyrosine kinase gene known as platelet-derived growth factor receptor B (PDGFB).

The continuing development of imatinib against different forms of (relatively rare) cancers is an interesting story that has important lessons for the future development of cancer therapy. Most notable is the fact that any given (small molecule) therapeutic agent will have a rich and varied pharmacology (other targets) within a cancer cell that was not necessarily part of the original project plan [1], and that this is not necessarily a bad thing in terms of potential clinical utility.

Making better use of existing agents

The often derided 'cytotoxic' class of anticancer agents, in large part the mainstay of cancer chemotherapy today, are still the subject of intense research and clinical efforts to improve patient outcome, often in combination with modern 'targeted' agents. An interesting new development on one such cytotoxic (DNA targeting) agent reported at this meeting was the identification of a genetic predictive test to identify brain tumour (glioblastoma) patients likely to respond to temozolomide, a cytotoxic agent licenced in 1999 for glioblastoma therapy.

The key to predicting patient response was found to lie in the methylation status of the DNA repair gene known as *O*-6-methylguanine-DNA methyltransferase (MGMT), with a methylated MGMT promoter being predictive for a significantly enhanced survival rate in the clinic. These new

data indicate that older established chemotherapeutic regimens are likely to still have a future role in cancer chemotherapy, albeit through the intelligent use of cancer biology knowledge accompanied by the modern 'omic' technologies.

The continuing emergence of new data that may have profound implications for the use of Iressa® in lung cancer treatment was touched upon at the meeting, and represents a further example of where detailed knowledge of drug target status (mutated EGFR in this case) [2] and patient response within tumour populations could lead to more rational and targeted use of anticancer drugs.

Conclusions

Advances in the field of molecular targets and cancer therapeutics have clearly lead to some important advances and successes in improving patient outcome in recently years. Despite the wealth of knowledge in cancer biology at the cellular level – translational cancer research – translating these advances into the identification of validated and tractable targets, and hence into new agents active in the clinic, is still a slow and often laborious process. It is clear from this excellent and thought-provoking conference that no-one yet knows the best way forward towards the discovery of new agents active in the clinic against the most common life-threatening solid tumours. Terms such as 'multitargeted', 'targeted', 'molecules to medicines', 'surprising targets', and 'rational approaches to the use of existing agents' were recurrent themes throughout the meeting. Having said this, considerable advances in the field in recent years give much cause for optimism.

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