New directions in cancer drug development

Joanne Clough, j.clough@elsevier.com

The recent SMi conference *Cancer Drug Development: New Directions and Challenges*, held in London, UK, on 10–11 March 2003, addressed the recent developments in therapies for cancer and looked towards the potential future breakthroughs, with presentations from leaders in the field. This review presents a few selected highlights.

Translational research

Karol Sikora (AstraZeneca; http://www.astrazeneca.com) chaired the first day of the conference and also kicked off with a presentation on translational cancer research as the key to the future. The global cancer market is set to triple by 2010 with many new drug applications (NDAs) for molecular therapies [1]. The new versus the old style of Phase I drug development for cancer using the maximum effective dose (MED) rather than the maximum tolerated dose (MTD) and determining the surrogate endpoint as a substitute measure of benefit, were discussed. Translational research is a problem for big pharma because access to body parts is limited and it will take the next 10 years until we have a better understanding of how to develop novel drugs. Sikora rounded up with the future industry needs as being access to tissues within an ethical framework, novel ideas for target identification, to get drugs to market fast and to make a return on investment.

Public policy: submissions and withdrawals

A personal view of NICE (http://www.nice.org.uk) and getting things right with submissions, was given by Paul Quartey (Schering-Plough; http://www.schering-plough.com), who spoke about his most recent submission with the drug Caelyx, a doxorubicin HCl liposome injection. Caelyx is used as treatment for advanced ovarian cancer in women who have failed first-line platinum-based chemotherapy. According to Quartey, the key to getting it right with a NICE submission is having the right drug and telling the right story, hopefully finding a patient population – a 'sweet spot' – well fitted for the therapy.

Alan Barge from AstraZeneca told the story of Iressa® (gefitinib), the first of a new type of cancer medicine for lung cancer (or non-small cell lung carcinoma; NSCLC). The mortality rate for lung cancer is practically 100%; most tumours are epithelial and epidermal growth factor receptor (EGFR) is the target of anti-NSCLC drugs. Iressa® is a small-molecule inhibitor of EGFR-TK1 (the Erb1 receptor). Recent data has suggested that Iressa® could have potential use in breast cancer and to target the EGFR in colon cancer.

New approaches, new drugs, new criteria

General considerations for novel approaches to the development of drugs for cancer were presented by Giorgio Massimini (Pharmacia; http://www.pharmacia.com). Development is mainly still focussed on single-agents and Massimini reiterated what had been said previously by Sikora about the MTD being an outdated endpoint and whether a more realistic endpoint would be the biologically effective dose (BED). He also described the shifting paradigms in clinical development from disease to target orientation and the assessment of combination therapy of new drugs with traditional ones.

Oncolytic viruses

Leonard Post from Onyx Pharmaceuticals (http://www.onyx-pharm.com) described the oncolytic virus approach to replicating viruses for cancer therapy. Replicating viruses can have two mechanisms: (1) direct cell killing by virus replication and (2) delivery of a therapeutic gene. DNA virus replication and carcinogenesis require inactivation of the same cellular defence mechanisms. The compound ONYX015 kills tumour cells by virus replication; it does not deliver inserted genes and thus is not gene therapy. Monotherapy and combination therapy showed proof-of-feasibility for the systemic delivery or selectively replicating adenovirus. Onyx's technology for the intravenous administration and tumour-specific delivery of a gene product is known as ATV™ (Armed Therapeutic Virus™) technology.

In a similar vein, Robert Coffin from Biovex (http://www.biovex.com) spoke about oncolytic herpes viruses and cancer immunotherapy using the model herpes simplex virus (HSV). Biovex's OncoVEX$^{GM\text{-}CSF}$ combines oncolysis with the granulocyte macrophage-colony stimulating factor (GM-CSF) and is a dendritic cell (DC)-mediated vaccine. The aim of this type of therapy is to increase anti-tumour effects by including a therapeutic gene, and improved killing of colorectal carcinoma cells was observed.

Imaging technologies

Bringing Diagnosis and Therapy Together was the subheading of the presentation by Jonathan Allis from Amersham

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Health (http://www.amershamhealth.com) who stressed the importance of imaging in cancer diagnosis and treatment. A comparison of the different imaging technologies was given, including ultrasound, magnetic resonance (MR), optical and particularly positron emission tomography (PET). PET is of particular importance in drug discovery and cancer diagnosis because almost any drug can be labelled with ^{15}O, ^{11}C, ^{18}F or ^{15}N, enabling the drug to be followed in the body; thus, receptor binding potential can be determined and the mechanism-of-action can be established.

The IMiDs

Jerome Zeldis from Celgene (http://www.celgene.com) spoke about immune modulatory drugs – the IMiDs™ – and the potential of other new therapeutics, including SelCIDs, JNK inhibitors and E3 ligase inhibitors. IMiDs are thalidomide-like in their action and potential activities include inhibition of TNFα induction, anti-angiogenesis, immune stimulation/modulation and cell cycle effects. Thalomid®, the first commercialized IMiD, has numerous investigational uses, including those for HIV, cancer, dermatology, neurology and infectious diseases.

From genes to drugs

Sir David Lane (Cyclacel; http://www.cyclacel.com) started the presentations on the second day of the conference, which was chaired by Jim Cassidy (Professor of Oncology at Cancer Research UK; http://www.cancerresearchuk.org), with a talk on cell cycle control and choosing the right targets. The focus was on the cyclin-dependent kinases (CDKs), their regulation, and why they are targeted for cancer therapy. Small protein CDK inhibitors are induced by tumour suppressors; p21 is an inhibitor that targets CDKs, and p27 is a natural inhibitor of the cyclin A–CDK complex. Cyclacel's compound CYC202, which has antitumour activity against a variety of tumours, has a biomarker in p53 induction. Lane spoke about cancer cell mitosis as a target for anticancer drug discovery and the mitotic spindle as a target for cancer therapeutics.

DNA mechanisms as novel targets

As introduced briefly by Lane, the mitotic spindle is a target for cancer therapy, as presented by Pearl Huang (GlaxoSmithKline; http://www.gsk.com). There are 47 human kinesins that are involved with cell cycle specificity. The kinesin spindle protein (KSP) drives centrosome separation by sliding antiparallel microtubules. The expression of KSP was found to be increased in tumours relative to normal tissue. Inhibitors of KSP (KSPI) block centrosome separation and induce mitotic arrest. An *in vivo* study on human ovarian cancer with KSPI showed improved activity relative to Taxol. Thus, mitotic kinesins are validated targets.

Steve Jackson (Kudos Pharmaceuticals; http://www.kudospharma.co.uk/ Wellcome Trust/CRUK) talked about a new target for cancer therapy in the form of DNA repair and drugs that inhibit this process. This is a major field of research and could have broad use against multiple cancers, as well as applications in other diseases. DNA-dependent protein kinases mediate DNA double-strand break repair and DNA repair pathways are the Achille's heel of most cancers.

Targeted molecular therapy

Is the era of cytotoxics over? was the title of the presentation by Jorge Otero from Lilly (http://www.lilly.com), who talked about the use of cytotoxic agents over the past 15–20 years; recent experiences with targeted therapies have improved outcomes over traditional cisplatin/Pt-based therapies. Progress has been made with drugs such as Herceptin and Gleevec but setbacks have included Marimastat and Iressa (mentioned previously). Conclusions were that this era is not truly over but lessons must be learnt from targeted agents.

Signal transduction inhibition – protein kinase inhibitors with broad therapeutic potential – was described by Peter Traxler (Novartis; http://www.novartis.com). The importance of tyrosine kinases (TKs) in human cancer was discussed, as was the target-directed drug design of inhibitors of EGFRK, VEGFRK, Bcr–Abl/KitK and Flt3K and also the ideal profile of a TK inhibitor. However, it is apparent that the future challenges are great: these include improving the predictibility of preclinical animal models for the development of biomarkers and the design of Phase I trials, and overcoming resistance mechanisms, such as efflux pumps and point mutations.

Polyketide drug candidates was the subject of Richard Hutchinson's (Kosan Biosciences; http://www.kosan.com) presentation. Polyketides are small, orally active molecules found in soil micro-organisms and are a rich source of pharmaceuticals. The compounds epothilone D and geldanamycin were described as anti-cancer agents with geldanmycin having potent anti-cancer activity and targeting Hsp90 (a protein chaperone).

Concluding remarks

This conference brought together many different aspects of cancer therapy from old drugs to new targets and where the future challenges and directions in cancer therapeutics lie. The SMi *Clinical Trials in Cancer* conference is to be held on 11–12 June 2003, London, UK (see http://www.smi-online.co.uk/cancer3.asp for details).

Reference

1 Sikora, K. (2002) Surrogate endpoints in cancer drug development. *Drug Discov. Today* 7, 951–956