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Paying for the next generation of antimicrobials

In response to the editorial by Coast and Smith in a recent issue of *Drug Discovery Today* [1], I hope I am not dependent on the authors to deliver protection from methicillin resistant *Staphylococcus aureus* when I come to need it. The past sixty years has seen the successful development of new treatments by profit-driven private companies, and the accompanying failure of 'directly undertaking...R&D...' [1] to deliver marketable results. The 'collective action... for the reform of international patent laws...' suggested by the authors would ensure that few new molecules would be developed to meet the needs of either wealthy or poor countries.

New ideas and investment are needed if we are to keep ahead of microbial resistance, and there are some inappropriate incentives currently in place that are having undesirable results: (1) buyers have exploited the competitive market to drive down the price of classic antibiotics to the point where 'depreciation' of antibiotics (the spread of resistance) is not covered; and (2) hospitals have exploited these cheap antibiotics to save money on hygiene and patient isolation.

The cost of developing new drugs has been increasing at a median compound annual growth rate of 6% for at least the past nine years [2]. This is partly an indicator of the demand for talented researchers and trained investigators who, without the right incentives, will choose to work in therapeutic areas other than antimicrobials research.

A combination of policies is needed to deliver progress in this area: increased hospital expenditure on hygiene and patient isolation; increased use of 'expensive' new antimicrobials; increased patent protection for new antimicrobials in exchange for limits on use; and increased investment in understanding the biology of resistance.

A recent report (Scrip, No. 2813, 8th January, 2003) suggested that a new generation of antibacterials, including quinolones, carbapenems, oxalidinones, peptide deformaylase, isopentenyl pyrophosphate biosythesis inhibitors and triazole antifungals, are being developed. The pharmaceutical industry seems to be responding but low share prices suggest that there are doubts about the wisdom of current R&D investment levels. Hospitals and other public and private bodies must now spend more to protect these new agents from resistance while maintaining incentives to invest.

References

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Anti-angiogenesis: biology is the foundation for therapy

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The SMi conference entitled *Angiogenesis*, which was held in London, UK, on 17–19 February 2003 focused on preclinical and clinical data of various compounds interfering with blood vessel formation in tumors, an approach also termed anti-angiogenesis. The meeting provided an excellent overview regarding the latest technology development aimed at better understanding the complex biology of tumor growth and angiogenesis.

The central role of VEGF

The central role of the vascular endothelial growth factor (VEGF) during pathologic angiogenesis, combined with its restricted expression in healthy adults, has spurred the development of a variety of therapeutic strategies aimed at blocking VEGF or VEGF-induced signal transduction (reviewed in [1]). Thus, about half of the presentations focused on the clinical development of compounds targeting VEGF or signaling events induced by the VEGF receptors.

The compounds discussed included monoclonal antibodies, soluble receptor chimeras and small molecule inhibitors

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targeting the VEGF-receptor tyrosine kinase domains. The remaining talks focused on novel technologies, including DNA arrays to study changes in gene expression during angiogenesis. Recent developments regarding novel *in vivo* models, such as zebrafish (as presented by Chaoyong Ma, Phylonix; http://www.phylonix.com), to rapidly identify potential angiogenic genes, as well as novel imaging technologies to monitor vascular changes during pro- or anti-angiogenic treatments, were also discussed.

Compounds targeting VEGF or VEGF-induced signal transduction pathways

Most anti-angiogenic compounds that were presented displayed profound inhibitory effects on tumor growth, metastasis or vascular permeability when tested in preclinical models [presentations by: Francesc Mitjans, Merck Farma y Quimica (http://www.merck.com); Claire Lewis, BioActa; Jocelyn Holash, Regeneron Pharmaceuticals (http://www.regeneron.com); David Stirling, Celgene (http://www.celgene.com)].

Data presented from Phase I dose-escalation studies indicated generally mild adverse events and common side effects, included diarrhea and hypertension [Steve Wedge, AstraZeneca (http://www.astrazeneca.com); Gregory Roberts, Pfizer (http://www.pfizer.com)]. However, there is some limited preclinical and clinical evidence that certain tumors might eventually find a way around single anti-VEGF/VEGFR strategies [Hans-Peter Gerber, Genentech (http://www.gene.com)]. Such 'tumor escape' was most pronounced when treatment was initiated at later stages during tumor growth. The clinical data further indicated some potential differences in toxicity profiles between different compounds. For some small molecules, but not all, increased levels of thrombocytopenia, neutropenia or fatigue was observed when administered in combination with cytotoxic agents, and was dose limiting in some cases (reviewed in [2]).

These observations could represent a consequence of interfering with certain biological functions of the VEGF/VEGFR signaling axis and could be caused by individual differences in pharmacological and/or pharmacodynamic properties of the compounds tested. Alternatively, unspecific inhibition of unknown tyrosine kinases might be contributing to the variations in their safety profiles. In this case, the toxicity would be unrelated to the intended mechanism-of-action, which represents the Achilles' heel of this class of compounds. In this regard, antibodies blocking only one angiogenic target might be less prone to such non-mechanism related toxicities. The central question that arose from these observations was which of the two strategies, targeting one or multiple angiogenic pathways, might turn out to be most successful in the clinic?

Questions and answers

An answer to this all important question could eventually be deduced from some of the data presented at this conference. Blocking VEGFR-1 in mice by means of a highly selective monoclonal antibody was beneficial in a variety of disease models associated with neo-angiogenesis in mice [3]. However, according to Peter Bohlen (ImClone Systems; http://www.imclone.com), the same antibody inhibited bone marrow recovery and increased lethality in mice when administred in combination with cytotoxic regimens known to induced bone marrow ablation (see [2]). Combined, these examples suggested that neither strategy on its own has an intrinsic advantage, and that understanding the complex biology might be the key determinant for success.

The most efficient anti-angiogenic strategies could eventually be determined by the ability of a compound to interfere minimally with essential physiologic functions and to block pathologic angiogenesis maximally in a tumor- and treatment-specific context. The chemical class, pharmacokinetic properties and potential pharmacological interaction between multiple drugs, when administered in combination, might add to the complexity already provided by the biology.

New technologies to identify and characterize novel pro- and anti-angiogenic compounds

The strong correlation between hypoxia, VEGF expression and pathologic angiogenesis suggested that genes regulated by VEGF and/or hypoxia in endothelial cells could potentially be used as therapeutic targets or markers within pathologic vasculature (David Sherris, Sherris Pharma Partners). Thus, several speakers focused on the identification of novel genes regulated by VEGF and/or hypoxia in endothelial cells.

Catherine Tribouley (Incyte Genomics; http://www.incyte.com) described the approach of using laser capture micro-dissection (LCM) technology in combination with cDNA-arrays to identify genes specifically up-regulated within tumor vasculature. This technology is based on the selective isolation of endothelial cell RNA from tumor tissues and thus could lead to the identification of tumor vasculature specific antigens or other potential therapeutic targets, and some candidates were presented.

A different approach, presented by Stuart Naylor from Oxford BioMedica (http://www.oxfordbiomedica.co.uk) led to the identification of a panel of genes potentially involved in pathologic angiogenesis based on their inducibility by transcription factors mediating

hypoxic responses, such as hypoxia inducible factor 1 and 2 (HIF1 and 2). Although the data presented was encouraging, their relevance for tumor angiogenesis *in vivo* remains to be determined.

Monitoring vascular changes during anti-angiogenic treatment

The primary target of anti-angiogenic therapies is the vasculature and thus it was somewhat surprising to learn how little is known about the changes occurring within the vasculature of tumors treated with anti-angiogenic compounds.

Many of the current imaging methodologies are not standardized and none of the imaging tests described so far is validated as accurate surrogate markers of angiogenesis. By contrast, the positron emission tomography (PET) technology presented by King Li (Radiology and Imaging Sciences, National Institutes of Health; http://www.nih.gov) does enable the quantification of absolute physiologic parameters, such as tumor perfusion, blood volume and capillary permeability. This could be instrumental in the investigation of the mechanism-of-action or the optimal dose of anti-angiogenic compounds, which is an intensively debated topic within this area of research.

Finally, a novel image guided genomics and proteomics approach was presented (King Li) wherein specific regions within a tumor were identified using imaging techniques. Tissue within these regions were subsequently isolated and analyzed for specific gene expression patterns by DNA arrays and protein expression by protein profiling techniques.

Concluding remarks: angiogenesis the future

In conclusion, the discovery of novel pro- and anti-angiogenic factors or genes that are specifically regulated in endothelial cells within pathologic vasculature is important, both for advancing our basic understanding of cell regulation and for providing novel targets for drug discovery. Better understanding of the molecular mechanism and the biological and physiological consequences associated with blocking blood vessel formation will be helpful to accelerate clinical development and basic research and to improve the treatment modalities aimed at interfering with pathological angiogenesis.

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