The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Joanna Owens, Acting News & Features Editor, *Drug Discovery Today*, e-mail: Joanna.Owens@elsevier.com

Current understanding of mistletoe lectins ▼

A recent letter in *Drug Discovery Today* [1] by Li pointed out that aqueous mistletoe extracts have been used as a complementary cancer drug for almost a century. With recent advances in biochemistry and molecular biology, new approaches have been used to study their anti-cancer effects. The main biological activity of the extracts has now been attributed to the mistletoe lectins (MLs). So far, one ML gene has been cloned from the European mistletoe (*Viscum album*) [2]. However, three ML chains with slightly different carbohydrate recognizing specificities and molecular weights have been isolated [3]. In addition to the European MLs, a Korean counterpart has been isolated from the subspecies (*V. album coloratum*) [4].

All of these MLs consist of a toxophoric A-chain and a carbohydrate recognizing B-chain. The A-chain is an RNA-glycosidase, which cleaves the rRNA at a specific site effectively inhibiting protein biosynthesis. Binding and internalization of MLs into cells are mediated by the B-chain, thus they are classified as type II ribosomal inactivating proteins (RIPs) [5].

Lyu [6] recently showed that the Korean ML also acts as an inhibitor of telomerase, whereas the Bax protein, an enhancer of apoptosis, is upregulated in ML-treated cells. Beyond its relevance for cancer research, this finding is also of interest for basic cell biology. It indicates that, despite the inhibition of protein synthesis by the RNA glycosidase activity of ML, there must be a mechanism, that enables protein biosynthesis for the proapoptotic proteins to continue. How this effect is achieved remains unclear, as does the question of how the bulky ML protein is transferred from the endocytotic vesicle across the lipid bilayer once it has been internalized. This transfer is a prerequisite for the action of ML on the ribosome, which is either in the cytoplasm or attached to the membrane of the rough endoplasmic reticulum.

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Udo Schumacher and Ursula Valentiner
Institute for Anatomy
University Hospital Hamburg-Eppendorf
Martinistrasse 52
D-20246 Hamburg
Germany

Polymers for drug delivery: more research needed ▼

The use of polymers in drug delivery continues to increase as clinical results show therapeutic benefits, novel applications are discovered and sources of polymers and their derivatives become more accessible. Polymers such as polyethyleneglycol and poly(styrene-co-maleic acid) now enjoy an integral role in drug delivery formulations available on the market. Yet it remains true that the biological effects of even 'biocompatible' polymers are largely unknown, perhaps because such effects seem pale in comparison to those of the drug that the polymer is helping to deliver, especially in cases where the polymer serves to mask unwanted biological responses to the drug.

It is nevertheless important to state that the biological effects of polymers should not be discounted when considering either the efficacy or safety of the whole formulation. One issue that has been particularly neglected is the effect of systemically applying polymers that are not truly biodegradable, but are too large to be cleared by renal filtration, and which will almost certainly be retained in the body long after the drug has gone.

Chemists now have the tools that make possible screening of a range of

polymer chemistries to reduce unwanted biological effects. In addition, monodisperse polymer preparations are beginning to emerge in the form of dendrimers [1] and polyamides [2] and the field should soon witness an increase in the molecular weights of these preparations such that they become useful in drug delivery. Methods for the facile preparation of such polymers would assist in the rational characterization of the biological effects of polymers and enable more rapid design and development of polymers toward desired therapeutic goals.

Although the biological effects of apparently innocent polymers are unknown and monodisperse polymer preparations are unavailable, Hunter and Moghimi [3] are correct to call for more work in these areas and suggest that the field of polymer therapeutics will otherwise take a long time to reach its full potential.

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Ross O. Phillips
ML Laboratories plc
Stephenson Building
Science Park, Keele
Staffordshire, UK ST5 5SP
e-mail: ross.phillips@mlresearch.co.uk

Pharmaceutical companies need to broaden research

Attending the 14th International Genome Sequencing and Analysis Conference in Boston (2–5 October 2002) made me wonder whether pharmaceutical companies are taking advantage of the latest developments in mammalian, model-organism and microbial genomics. I will limit myself to three examples from the meeting.

Kelly Frazer of Perlegen Sciences (http://www.perlegen.com/) commented that numerous novel human transcripts are not conserved in the mouse, and cited examples of novel transcripts with intriguing origins (e.g. a breast cancer cell line) and even more intriguing structures (e.g. endogenous cis-antisense to a known protein-coding gene).

Victor Ambros of the Dartmouth Medical School (http://www.dartmouth.edu/dms/) spoke about the importance of noncoding micro-RNAs in *Caenorhabditis elegans* gene expression regulation, and noted that several developmentally regulated micro-RNA candidates are not conserved in the related worm *C. briggsae*.

David Relman of Stanford University (http://www.stanford.edu/) reported that over 1500 species of bacteria (and, surprisingly, even archaea) found in human subgingival crevices are novel and that disrupted microbial ecologies are likely to be relevant not only to gingivitis, but also to more serious conditions such as inflammatory bowel disease. These findings underscore the need for a human 'environmental genome' (microbiome survey) project.

Given these developments, why do many in the industry limit their database mining efforts to the identification of evolutionarily conserved proteins? Why is the lack of research on non-conserved, and non-protein, targets seldom lamented? Perhaps most importantly, why is work on the pathogenesis of common human diseases largely synonymous with analyzing human SNPs, or with identifying 'druggable' protein targets of human origin, when it is becoming increasingly clear that all genetic material and all proteins found on and in the human body – regardless of whether their origin is human or microbial – might be relevant to the pathogenesis of these common conditions? After all, treatments for common, mixed-etiology disorders are precisely what post-genomic medicine has promised, and so far failed, to deliver.

Leonard Lipovich
Dr. Mary-Claire King's laboratory
Dept of Genome Sciences
University of Washington
1959 NE Pacific Street, MS 357730
Seattle WA 98195-7730, USA
e-mail: LL@u.washington.edu

Corrigendum

Please note a correction to the article *Mining the human 'kinome'* by David A. Dunn, published in *Drug Discovery Today*, 15th November 2002, Volume 7, No. 22, 1121–1123.

On page 1122, in the second column, the article references the company Kinexis: this should have read Kinexus, and the correct web address for this company is http://www.kinexus.ca.

We would like to apologize for this inaccuracy and for any confusion that this might have caused.

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