suppressing and interleukin-10 (IL-10) augmenting activities. The dual-acting molecule was developed from an initial CNS lead that had nanomolar affinities not only for TNF-α and IL-10 targets, but also for dopamine-2, 5-hydroxytryptamine (HT)-1A, 5-HT_2 and 5-HT_1 receptor preparations.

In conclusion, the preparation of dual- or multiple-ligands on an almost rational basis is now conceivable and it can be expected that many of these molecules will yield drugs of superior clinical value compared with monotarget formulations.

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Trends in the use of ultrasound-mediated transdermal drug delivery

The skin is an appealing route for the delivery of drugs because it offers the efficacy of injection with an ease of use that is comparable with oral administration. However, transdermal drug delivery is limited to those drugs that comprise small molecules (<500 Da). Consequently, emerging techniques that have the potential to increase the number of drugs that could be administered by this route are the focus of extensive research. There are various enhancers, for example, chemicals and electrical current (iontophoresis and electroporation), that are currently being investigated as methods for improving the transdermal delivery of drugs. An additional enhancer that has received considerable attention is the use of ultrasound (sonophoresis), a topic that was addressed by Lavon and Kost [1] in a recent issue of *Drug Discovery Today*.

Since the initial results reported by Fellinger [2], the efficacy of ultrasound has been widely demonstrated with small and large molecules. Today, the delivery of large molecules (e.g. insulin) at low frequency ultrasound (<100 kHz) has encouraged a greater interest in increasing skin permeability [3–5]. Moreover, the use of ultrasound has been extended to monitoring glucose levels in blood [6], which demonstrates that skin permeabilization via the application of ultrasound could enable the delivery of molecules to the body and facilitate the withdrawal of molecules from the body. The interest in ultrasound-mediated molecule delivery is thus based on two factors: (i) the capacity to enhance the efficacy of existing transdermal formulations (e.g. anesthetics and non-steroidal anti-inflammatory drugs) by improving the topical action of the drug; and (ii) the potential of sonophoresis for the improvement of patient compliance in therapeutic domains such as diabetes and psychiatry and also in the delivery of vaccines. With an increasing number of biomolecules emerging from biotechnology, the choice of the best route of administration is becoming crucial, and the transdermal mode appears to be an excellent candidate in some cases (e.g. treatment of psoriasis).

One of the key issues for the success of sonophoresis technology remains the development of low cost ultrasound devices that enable efficient transdermal drug delivery. Although low-frequency sonophoresis has been extensively studied in the past ten years, there are no low-frequency sonophoresis devices commercially available today. The principal difficulty lies in the development of a miniaturized low-frequency ultrasound device that is powerful enough to create pathways within the skin. There are two prototypes of low-frequency sonophoresis devices for which preliminary human pilot trials have already been conducted. An ultrasonic skin-permeation instrument [SonoPrep® (Sontra Medical; http://www.sontra.com)] was used in a Phase I clinical study performed in patients with diabetes [7]. In another study, rapid cutaneous anesthesia (5 min) was achieved after pretreatment with the SonoPrep® (10 s) followed by application of EMLA® cream (AstraZeneca; http://www.astra.com) [8]. Transdermal insulin delivery has been achieved in a preliminary human pilot trial using a device developed by Encapsulation Systems (EX1–4; http://www.encsys.com) that comprises a four-element transducer array containing a special cymbal transducer.

Research using sonophoresis and other chemical or physical enhancers has significantly advanced knowledge on the structure and function of the skin. However, the primary role of the skin is to protect the body against the environment and, therefore, one of the questions that remains concerns the long-term biological effects of multiple ultrasound applications at the same site of the body in terms of skin physiology. This emphasizes the need to perform further skin tolerance studies to

determine standards for this new application of ultrasound.

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Cell-based screening

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The 11th annual *Cell-Based Assays for HTS* meeting, which was organized by the Cambridge Healthtech Institute (http://www.healthtech.com) as part of the *World Pharmaceutical Congress* (17–19 May 2004, Philadelphia, USA), brought together over 100 delegates, including representatives from the pharmaceutical industry and the technology provider sector, to hear experts describe the progress made in cell-based screening, and to discuss the advantages and disadvantages of this technology over cell-free screening. As well as case studies on molecular target screening and 'pathway screening', there were several presentations on emerging technologies. In two lively panel discussions, the major aspects of cell-based screening and assay miniaturization were addressed.

Molecular target screening

Lisa Minor (Johnson & Johnson; http://www.jnj.com) highlighted some of the cell-based methods that have been used for the screening of membrane tyrosine kinases. Growth-factor receptor tyrosine kinases are typically screened with biochemical assays in which only the kinase domain, and not the complete protein, is used. However, agonists or small-molecule mimetics can only be found with cell-based screens. Minor explained how fluorescence methods, such as dissociation-enhanced lanthanide fluoroimmunoassay [DELFIA© (PerkinElmer; http://www.perkinelmer.com)], enable the sensitive measurement of insulin tyrosine kinase phosphorylation in cells.

Cell-based assays are used to screen targets that are refractory to biochemical purification, such as G-protein-coupled receptors (GPCRs) and ion channels. Gareth Waldron (Pfizer; http://www.pfizer.com) described the development of an assay to measure voltage-gated potassium channel activity using membrane-potential-sensitive fluorescent dyes and voltage–ion probe reader (VIPR) technology. Waldron emphasized the necessity of validating ion-channel assays, not only for statistical reproducibility, such as Z-factors [1], but also for the pharmacology of reference compounds (e.g. IC_{50}). In addition, it was reported that comparison of the results generated using VIPR and the patch-clamp technique demonstrates that there is a good correlation between these two methods.

Guido Zaman (NV Organon; http://www.organon.com) described assays for the identification of agonists, antagonists and selective modulators of steroid hormone receptors. Cell-based luciferase reporter assays have been used to identify non-steroidal agonists and antagonists of the classical hormone receptors. The potency and efficacy of these ligands is dependent on the specific cellular environment, and could be influenced by the level of receptor expression. By contrast, radioligand-binding assays enable precise affinity determinations, and are indispensable for the assessment of the selectivity of compounds over closely related receptors.

Functional GPCR assays enable the identification of compounds that have a variety of mechanisms of action. Miguel Garcia-Guzman of Vertex Pharmaceuticals (http://www.vrtx.com) described the use of β-lactamase reporter-gene technology to identify allosteric enhancers of the A_1 adenosine receptor and of selective agonists of the

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