# Discovery on a credit card?

## 'five million molecules per year available'

Exciting advances are being made in microplate technology, with the possibility of densities of up to 9,600 wells per plate [*Drug Discovery Today* (1997) 2, 174–175]. However, it seems that Orchid Biocomputer (Princeton, NJ, USA) have upped the ante.

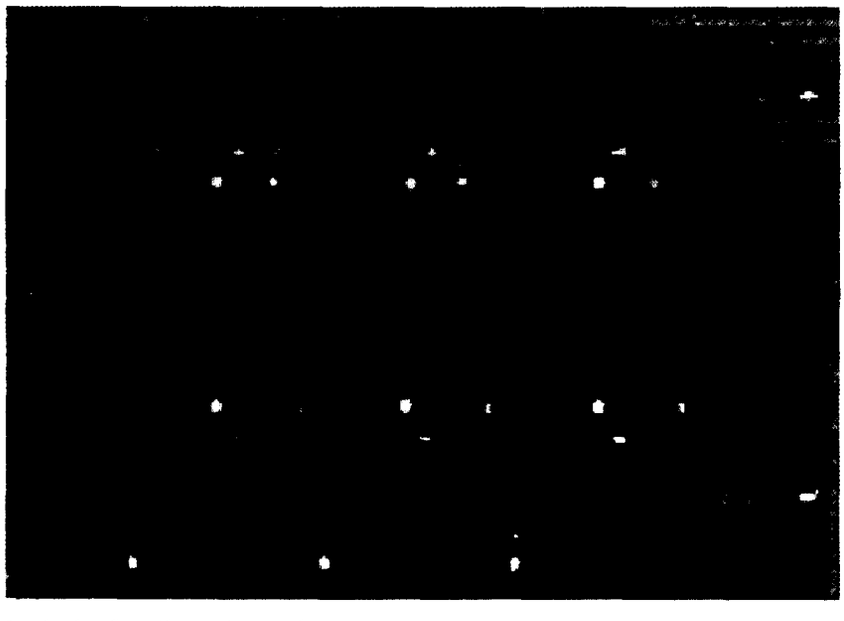
Orchid Computers is a joint venture between SmithKline Beecham (SB) and the Sarnoff Corporation (Princeton, NJ, USA), set up in September 1995. By 1998 Orchid plans to create a credit-card sized glass chip with 10,368 wells. The chip is much more complex than just a honeycombed piece of glass; it is the beginning of an integrated synthesis and detection device. Each well is 100 $\mu m^2$ and contains less than 1 µl in volume. To prevent evaporation, a glass sandwich was created in which the 'filling' is a chamber system. Connecting the wells are small channels that allow the shunting of reagents, synthesized compounds, or even cells to wells. Moving such minute volumes around is not an easy task, but Orchid has developed microfluidic pumps to achieve this. These pumps have no moving parts, but are in fact electronic pumps able to move small amounts of molecules based on their electric charge (electrohydrodynamics).

### Hitting the milestones

More than two years ago, the fabrication and microfluidic pumping systems were perfected and in November 1996 Orchid reached its first milestone with SB. This stage of development for the 10,000-well chip required microfluidic pumps able to support six of the reaction vessels (wells) (see Figure). The system is being developed in a modular way, so that blocks of functional reaction vessels can be pieced together like a jigsaw puzzle. With a planned budget of $15 million to spend in 1997 on R&D they soon hope to reach their second milestone: a 12 × 12 array of reaction vessels. The third milestone involves the final leap to the 10,368 array. Initially, the chip will be developed so that testing and detection devices are not part of the chip itself. With second and third generation devices, the detection apparatus will be built into the chip to form an integrated synthesis-and-detection device.

Synthesis is primarily carried out using solid-supports with one molecule per well, but there is no reason why synthesis cannot be performed without the aid of a support. Furthermore, the system could easily be adapted for synthesis of several compounds per well. To make easy deconvolution of lead compounds possible, a computer tracking system is being developed that controls the synthesis process. But can enough be synthesized in each well for testing purposes? According to Dr Dale Pfost, CEO at Orchid, nanogram quantities of material can be synthesized in each well to yield micromolar concentrations. The system can easily be integrated with a mass spectrometer hybrid, and tens of analyses can be performed to identify molecular structures. Orchid is working with SB and others to reformat standard assays to a microfluidic format that uses a fluorescence-based detection system under development at the Sarnoff Corporation.

What are the applications for such a device? Combinatorial chemistry and high-throughput screening will be the predominant uses for this technology. Because the device can be used for the synthesis of different molecules in each well, it could also provide a simple alternative to some of the DNA chips being developed by companies such as Affymetrix (Santa Clara, CA, USA). According to Pfost, DNA synthesis could easily be scaled down and performed in their chips using conventional solid-phase techniques. Furthermore, novel DNA chemistry being developed by companies such as NeXstar (Boulder, CO, USA) that uses both solution and solid-phase synthesis requires smaller quantities of reagents. This would be



*Orchid's 6-well synthesis chip.*



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beneficial if DNA is to be synthesized on a much smaller scale. Performing DNA synthesis in Orchid's chips in such a large array (10,368 wells) would be much more flexible than the complex photolithography used in the construction of other DNA chips.

### Biosensor applications

Orchid's device can also be used with intact cells. In fact, Orchid is working with DARPA (Defense Advanced Research Projects Agency, USA) to create biological-threat detection systems (biosensors to detect biological warfare agents). Taking this to extremes, the potential to grow cells such as neurons compartmentalized in wells and interconnected via the channels could in fact form the foundation for biocomputers. Perhaps one day, we will be using *n*th generation devices to grow 'real' neural nets used to replace damaged brain cells or even for 'upgrading' ourselves. But, enough of the science fiction.

With respect to future collaborations, Pfost divulges that they have had more than 60 meetings with major companies. Because of the great interest Orchid has attracted, the company is building a consortium for high-throughput screening, and they hope it will drive new standards through collaboration with instrumentation companies.

A device such as Orchid's 'credit card' is likely to cause a shift from the use of standard microplates to small high-density integrated systems for many applications. However, the device has yet to be tested to establish whether it can outperform its microplate ancestors, but it will not be long before the old and new formats find their niches in the modern day drug discovery laboratory.

*Martin Leach*

# Peptidomimetics and small molecule design

In March, *Peptidomimetics and Small Molecule Design*, a conference on the discovery and development of small-molecule drugs, was organized by IBC for the fourth year. The meeting, held in Philadelphia this time, consisted of a two-day conference with a further one-day workshop on combinatorial approaches to small-molecule design. It had a broad perspective with respected speakers from both industry and academia. Topics ranged from aspects of the investigation of protein–protein interactions to the synthesis of peptidomimetics on an industrial scale.

### Protein–protein interactions

The conference was opened by Dr Nigel Beeley (Amylin Pharmaceuticals, San Diego, CA, USA), who discussed how small nonpeptide molecules that imitate proteins can be identified. One approach is to focus on the protein's binding motif. The surface area of the binding motif, which is the area that needs to be mimicked, is often of the size of a small molecule. Calmodulin, leptin and amylin are examples of proteins for which this approach works.

Amylin is co-secreted with insulin, controls the release of glucose from the stomach, and is important in the regulation of the blood sugar level. It is predicted to bind as a loop-helix-turn, and alanine scan data suggest that six non-contiguous amino acids are involved in receptor binding, two of which appear to trigger agonism. Screening of a 30,000-compound database identified four structurally distinct nonpeptide antagonist leads. With the aid of the binding model the antagonist leads are being modified in a combinatorial fashion to develop agonists with oral bioavailability.

A method for determining helix–helix interactions in the absence of an X-ray structure was presented by Dr Weislaw Kazmierski (Glaxo Wellcome, Research Triangle Park, NC, USA). He described a disulphide trapping approach in which covalent bonds are formed between cysteine residues on the helices, thus identifying which faces come together upon dimerization (Figure 1). This technique provides useful information for the design of small molecules that interfere with dimerization. Such molecules have therapeutic potential in a variety of disease states. For example, the gp41 protein of HIV (which serves as the transmembrane anchor for the receptor-binding protein gp120) functions as a dimer. Disruption of its dimerization process should lead to disruption of the virus–host binding process.

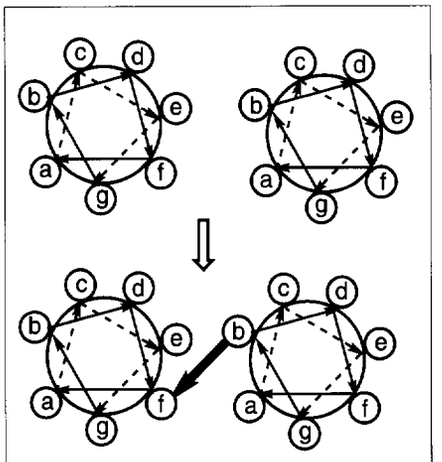


***Figure 1.*** *Dimerization of helices by the formation of a covalent bond between residues b and f.*

### Designed peptidomimetics

Prof. Victor Hruby (University of Arizona, Tucson, AZ, USA) described his approach to *de novo* design of stable, bioavailable ligands for G-protein-coupled receptors. The endogenous ligands for these receptors are unsuitable for examining biological function, or as drugs, because of their instability and lack of selectivity. Hruby's working hypothesis is that because the receptors are known to have considerable conformational homology,



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