come acquired Affymax, and the benefits are already apparent. The parent company's chemists from Research Triangle Park, Stevenage and Verona are being trained in solid-phase chemistry and automation at the Affymax sites in Palo Alto and Santa Clara. Stevenage chemists have already built two Affymax ESL synthesizers, which are now producing libraries; a similar technology transfer is also under way at Research Triangle Park. In addition, many Glaxo Wellcome biological screens have been transferred to Affymax.

One of Affymax's major attractions to Glaxo Wellcome was that its approach goes beyond organic chemistry: it integrates combinatorial chemistry with engineering and instrumentation associated with novel assay formats. Affymax is now charged with inventing enabling technologies for efficient drug discovery and transferring them to the rest of Glaxo Wellcome for exploitation. The combinatorial revolution has shaken up traditional

approaches to the final stages of lead optimization, and the Group's Combinatorial Lead Optimisation Programme is testing just how far down the drug discovery and development pathway the new technologies can be applied.

Lead optimization has traditionally relied on using single-compound synthesis, but this technique is rapidly being replaced by parallel synthesis of discrete compounds. One approach is array chemistry, a system involving dozens of parallel reactions for establishing structure/activity relationships. Glaxo Wellcome has developed proprietary parallel reactors, with efficient heating, cooling and stirring capability, and these

are spreading rapidly throughout the labs. Automated, and therefore faster, purification equipment has also been developed. Automated HPLC means that large batches of compounds can be purified each day, a previously unthinkable feat.

Glaxo Wellcome is equipping itself to remain the leader in combinatorial chemistry, and its latest research projects are heavily influenced by the new technology. But the traditional methods that served it so well in the past are not being abandoned. Instead, the company is testing the new technologies, and integrating those that work into its activities throughout its research laboratories. □
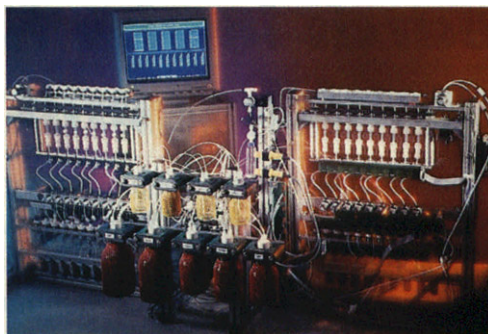
Systematization of research

Systematization of research follows naturally from the acceptance that knowledge gained from one drug target can be transferred to related targets. While hardly a startling concept, previous drug discovery projects tended to focus single-mindedly on one target. This concentrated minds on the matter at hand and led to many notable pharmacological successes, but it is an inadequate strategy for responding to today's biomedical opportunities. Systematization draws on knowledge of the human genome by combining advances in gene expression, automation, combinatorial chemistry and bioinformatics.

Over the past ten years, numerous families of genes have emerged. The majority of drug targets, however, come from only four of these:

- G-protein-coupled or seven-transmembrane-domain (7 TM) receptors (estimated total: 5,000)
- Nuclear (hormone) receptors (estimated total: >150)
- Ion channels (estimated total: 1,000s)
- Enzymes (estimated total uncertain because of low homology between members).

Of the top 100 pharmaceutical drugs, as defined by the International Marketing Survey audit sheets in 1995, 18 bind to 7 TM receptors, 10 to nuclear receptors and 16 to ion channels. The remainder generally inhibit enzymes.

The system-based approach attempts to transfer the knowledge gained from working on one drug target to other related targets. Much of the molecular technology required to work with one 7 TM receptor, for example, is useful for other 7 TM

receptors, including cloning and expression systems, together with information about their structures and ligands.

Systematization requires a significant commitment of time and resources. It allows efficiencies to be gained through economies of scale, but only if the target families are of significant size, richness and diversity of therapeutic value. For this reason, not all receptor and enzyme classes are candidates for this approach. In addition, a "learning opportunity" is created whereby past successes allow rapid attack on new targets.

At Glaxo Wellcome, the system-based approach is represented by two target classes in particular: 7 TM receptors and nuclear receptors. Both classes are appropriate, as they have already proven to be a rich source of valid drug targets with small-molecule ligands that are bioavailable, nontoxic and efficacious. In addition, generic technologies for the efficient discovery of new agonists and antagonists for these receptors are well advanced, and many validated targets within these receptor families remain for which no drugs currently exist.

Glaxo Wellcome already has leading drugs aimed at 7 TM receptors, including salmeterol (a β_2 adrenergic receptor agonist used to treat asthma), ranitidine (an H_2 receptor antagonist that blocks acid secretion), and sumatriptan (a $5HT_{1D}$ agonist for the treatment of migraine). The company thus has a database of molecules already directed at these proteins, making the chemistry necessary to reach untapped receptors particularly suitable for the new approach.

Unlike membrane-bound receptors, the

nuclear receptors are intracellular and control the activity of target genes directly. One of the first results of applying the systems-based approach to this class of target at Glaxo Wellcome has been the demonstration that thiazolidinediones are potent and selective activators of peroxisome proliferator-activated receptor γ (PPARγ), a nuclear receptor recently shown to function in adipogenesis.

Thiazolidinediones are known to have antidiabetic properties, increasing the insulin sensitivity of target tissues in animal models of non-insulin dependent diabetes mellitus. In vitro, they promote differentiation of preadipocyte and mesenchymal stem cell lines into adipocytes, but the molecular basis for this effect was unknown. The finding that they activate PPARγ not only provides the first known high-affinity ligand for the receptor, but also strongly suggests that PPARγ is a molecular target for the adipogenic effects of thiazolidinediones, as well as raising the possibility that PPARγ is a target for their therapeutic actions.

By using the systems-based approach, Glaxo Wellcome intends to be in a strong position to generate useful drugs against novel targets as they are discovered. It will also have access to a rich source of quality ligands for validating orphan receptor function. □