Isn't combinatorial chemistry just chemistry?

'The combinatorial revolution has had a greatly beneficial effect on chemical synthesis… but (this) has not been achieved by re-inventing chemistry.'

Ask someone what combinatorial chemistry means and you will probably get a variety of responses, ranging from messianic enthusiasm to luddite dismissal. What is incontrovertible, however, is that it was the chemistry phenomenon of the 1990s, resulting in more changes (and more hype) than any other new idea. In its wake spawned new departments, a vast array of technology, several start-up companies and a multitude of papers, books and even specialist journals. So what makes combinatorial chemistry special?

The aim

When it started about a decade ago along with HTS, combinatorial chemistry promised to turn drug discovery upside down. At first, the words 'library' and 'solid-phase chemistry' were introduced into the chemist's lexicon, and with them previously unimaginable numbers of compounds became accessible. Some people even suggested that the era of solution synthesis was over. Of course, there was also new technology, ranging from the credible to the plain ridiculous. In short, it seemed that a completely new branch of chemistry had emerged, which required a new outlook and practitioners with a new set of skills. New combinatorial groups were formed, and they were showered with generous budgets and told to get on with 'it' – whatever 'it' was.

For those involved, and I write as one, it was a terrifically exciting and creative time. Here was a blank piece of paper on which you could more or less write what you wanted, an unprecedented freedom for industry-based research. Because at that time combinatorial chemistry was so new, it was difficult to subject it to the checks and balances of other areas of discovery chemistry and, possibly for the first time, off-the-wall ideas were given a hearing, and occasionally support. The thesis was that combinatorial chemistry was the new 'ah-ha' factor, as in 'ah-ha, if we do this all our problems will be solved'. Chemistry was to be turned on its head and the drug discovery process reinvented, and hey-presto, pipelines would be choking with new chemical entities (NCEs).

The reality

However, to date, despite the millions invested, combinatorial chemistry has not delivered. With few exceptions, the new chemistry-changing technologies, when separated from the hype, have been disappointing and have had little impact on preclinical development. Why is this? The fundamental aim of the combinatorial revolution was to improve productivity to help fill the dwindling blockbuster pipelines. If a quantum leap in productivity was required, it was obviously much easier to believe that a major overhaul of 'traditional' chemistry by applying radical new technology was required, rather than some simple tinkering. However, the most successful use of combinatorial chemistry has tended to be from a higher throughput of the current process, particularly in optimization to select development candidates.

Nowadays, even the 'combinatorial' part of combinatorial chemistry is mostly extinct. Mixtures were an expedient way to get numbers, but now there are effective ways to generate large numbers without mixing. Solid-phase chemistry is in decline; the promise that the same benefits of peptide synthesis would spread to general organic synthesis has not been realized, and its limitations exposed. It always struck me as odd that a combinatorial chemist, who as a traditional chemist was trained to make white powders, was quite happy to believe that a brown smear in a vial (the usual result after resin cleavage) could be 100% pure. Although undoubtedly someone, with Everest-conquering perversity, will try to synthesize palliatoxin on a bead, the rest of the world moves back to solution chemistry. What has changed is efficiency. Great strides

Nick Hird, Discovery Research Laboratories, Takeda Chemical Industries, 17–85 Juso-Honmachi 2-Chome, Yodogawa-Ku, Osaka, 532-8686 Japan. tel: +81 66300 6819, fax: +81 66300 6085, e-mail: hird@lab.takeda.co.jp

 1359-6446/00/$ – see front matter PII: S1359-6446(00)01476-8

have been made using supported reagents and convenient work-up aids, and these will certainly influence chemistry practice. There has also been a tremendous impact from automation, both large and small. There is probably no chemist working in the laboratory now who does not routinely use some (probably simple) form of automation in their work. However, the development of synthesis automation has been a long struggle.

Synthetic chemistry requires the precise control of an environment and handling material in all three phases, a challenge for any engineer. At first, it was convenient to ignore this, and as a result the early instrumentation was not useful and not accepted. Now, designers have realized that the needs of the traditional chemist dictate the instrument and not the reverse, and the newer synthesizers are becoming firmly established in laboratories. Although, in many cases, usage of these instruments requires specialist training, it is probably the simpler tools that are making the greatest in-roads into enabling chemists to increase their productivity. Large-scale automation is also taking place, but it seems likely that the chemistry laboratory is not the best place to house this, and purpose-built compound factories could become as common as the scale-up facilities that already exist. As with these pilot plants, the compound factories will probably be operated on a 24 h basis, using operators rather than research chemists.

The future

So where does this leave the combinatorial chemist and the new technology? I am sure that the new technologies will significantly change the way we do chemistry, and possibly re-invent it – but not yet. There are the irresistible pressures of reduced cycle times and costs (both operational and environmental) that will act as drivers for miniaturization and virtualization. However, these technologies must be validated and shown to be an improvement on what is currently available before they will be assimilated. To my mind, this is still some way off.

The initial (and often lingering) hostility among traditional chemists towards combinatorial chemistry was borne out of over-optimistic claims and the idea that chemistry needed to be re-invented. Traditional chemists not only viewed it as a threat to their livelihoods, turning them from master craftsmen to compound-counting accountants, but were also, not unreasonably, skeptical of the claims. For example, you do not have to be R.B. Woodward to wonder how some of the early chip-synthesis technologies, which had difficulty with organic solvents, solids and non-ambient temperatures, were going to complete one synthesis let alone thousands. As the claims recede, and the proven tools, which are generally more recognizable and simpler, become widely assimilated into general practice, it is clear that there is nothing special or different about combinatorial chemistry.

There is no doubt that, despite its shortcomings, the combinatorial chemistry revolution has had a greatly beneficial effect on the evolution of chemical synthesis, but perhaps the time to consider it a special discipline, both organizationally and intellectually, is over. Probably the greatest impact of combinatorial chemistry has been the realization that productivity can and must be improved at the level of the individual chemist, as well as an improvement in the availability of the tools required to achieve this. However, this culture change has not been achieved by re-inventing chemistry, so why don't we drop the 'combinatorial' and call it 'high throughput' or 'automated' or, better still, just chemistry?

Nick Hird

HIV patent infringements...

Chiron Corporation (Emeryville, CA, USA) has won a patent infringement suit against **Hoffman-La-Roche** (Basel, Switzerland) in Dusseldorf, Germany. The federal district court issued a judgement finding that certain HIV polynucleotides used in Roche's HIV polymerase chain reaction (PCR) diagnostic tests infringe Chiron's EP0181150 patent that covers Amplicor™ and Amplicor Monitor™. Furthermore, the court ruled that Chiron is entitled to damages for Roche sales dating back to 1993 and can enjoin Roche from selling these products in Germany. This ruling is now subject to appeal. Roche has twice opposed the patent in the European Patent Office and initiated litigation in Germany, both of which failed, with a further (and possibly final) hearing before the Technical Board due to be scheduled. Chiron offered Roche a license under EP0181150, but was refused. Chiron therefore intends to enforce the injunction order.

VaxGen (Brisbane, CA, USA) has won a European patent dispute that was filed against them by **Chiron Corporation** (Emeryville, CA, USA). This patent, which was originally issued to Genentech in 1995, covers specific forms of the HIV envelope glycoproteins, gp160 and gp120, methods of purification and manufacturing the proteins, and their use for prophylaxis and treatment of HIV/AIDS. In the future, VaxGen anticipates licensing certain rights to these proteins to vaccine developers pursuing HIV/AIDS vaccines that use HIV envelope proteins in combination with DNA or live virus. Robert C. Nowinski, Chairman and Chief Executive of VaxGen said, 'Since most vaccines under development include HIV envelope proteins, these patents not only provide protection for our own vaccine but should enable VaxGen to participate financially in most other HIV/AIDS vaccines.'