long been interested in assembling nanoparticles into arrays, primarily through the use of crystal strain produced in layer composition to guide the formation of arsenic precipitates. Although the technique produced alignments in rows at a 100 Å scale, Kiehl found difficulties in achieving such alignments at the 10 Å scale, and dropped that particular avenue after encountering Seeman's research.

Going for gold

To demonstrate the viability of this approach to manufacturing electrical circuitry, Kiehl's team is investigating an assembly of gold nanoparticles into linear arrays on the DNA scaffolding. In their approach, a set of short DNA strands with different sequences are formed into DNA tiles that self-assemble into a DNA crystal. The particles are assembled onto the DNA scaffolding by covalently attaching the gold nanoparticles to a strand. In their recent tests, gold nanoparticles approximately 1 nm in diameter with a 4 nm interparticle spacing were assembled on a DNA scaffolding to form linear arrays, positioned 64 nm apart.

The contemplated 2D layout, which facilitates cooling on the chips interior far more than a 3D layout would, is consistent with the manner in which transistors are laid out on silicon chips. However, notes Kiehl, the development of a scheme for assembling scaffolding in more intricate 2D patterns, such as superlattices and periodic patterns, would promote flexibility in circuit design. Extending the structures to a third dimension, with multiple layers of 2D crystals, might enable the programmed self-alignment of sub-elements for integration of nanodevices or nanowiring for other functions, such as biasing and signal lines.

Presently, notes Kiehl, nanoparticle assembly on DNA scaffolds 'show just enough yield to demonstrate the technique is working'. Gold could be replaced with an electronic molecule with desirable characteristics, which would be suitable, for example, as a single electron tunneling device for processing or storing information.

The future

Kiehl sees a powerful future possible with this approach. Nanoparticles provide metallic islands for electronic memory storage, a technique that is compatible with periodic arrangement of nanoparticles on DNA scaffolding.

Nanoclusters that use the electrical phase of electron tunneling to represent logic state could ameliorate bigger challenges in improving information processing. Replacing conventional chip circuitry based on random interconnections of transistors, locally interconnected devices can emulate nonlinear dynamics similar to those in the human brain. DNA scaffolding with neuron-like and cellular network architectures thus portend storing and processing information technologies that are modeled on principles inspired by biological systems.

Cutting edge approaches to drug design

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The third *Cutting Edge Approaches to Drug Design* conference attracted over 100 visitors from the pharmaceutical industry and academia. Organized by the Royal Society of Chemistry, and held in London, UK, on 19 March 2003, what makes this topic so attractive?

The 'hole' in the drug development pipeline

Over the past four decades, annual R&D spending in US dollars increased 12-fold, with the yearly rate of NCE (new chemical entity) approvals by the US Food and Drug Administration (FDA; http://www.fda.gov) on average merely doubling from about 18 to 35 per year [1]. For one compound to hit the market, more than US$ 500 million and on average 12–15 years (depending on the target) had to be invested [2]. Fewer than 5% of all screened compounds enter preclinical development and only one out of five compounds that enter Phase I trials will make it through to the end [2]. But with the clinical testing causing 80% of the cost of a new drug, as few compounds as possible – only the most promising ones – should be admitted to clinical stages, thereby increasing the chance of overall success.

This is where *in vivo* and *in vitro* techniques meet *in silico* approaches. Algorithms are employed to predict bioactivity, ADME and possible toxic effects of either existing compounds – or even just virtually synthesized ones. Thereby, attempts are made to increase success rates by using 'cheap' computer power, compared to experimental work. Computer algorithms can also be employed in an earlier stage, in selecting suitable targets, using the wealth of data created by the recently finished genome initiatives.

The power of grid computing

After a general introduction by Darren Flower (Edward Jenner Institute for Vaccine Research; http://www.jenner.ac.uk), Graham Richards from the University of Oxford (http://www.oxford.ac.uk) gave the keynote lecture on his grid-computing project, employing over 2 million PCs in more than

1478-5282/03/$ – see front matter PII: S1478-5282(03)02305-5

200 countries to find molecules – from a 3.5 billion molecule database – that are involved in the pathogenesis of cancer and anthrax [3]. Effectively having the computer power of a 100 teraflop machine, they spent the equivalent of 200,000 years computing time on identifying unknown binding sites of several dozen targets and, mainly, screening their library using a three- and four-point pharmacophore description. The multi-scale approach (single-point molecule to more complex representations of the ligands) for the identification of binding sites, developed by his former collaborator Daniel Robinson [4], seems worth mentioning here.

Bioinformatics in target identification

Neera Borkakoti (Medivir UK; http://www.medivir.co.uk) now switched to the bioinformatics side, showing us how the wealth of genomic data can be used to select suitable targets; for example, by identifying target genes without orthologues in the patient in an attempt to minimize side effects. Borkakoti also made clear the goal we are heading towards, and that is a specifically tailored drug to both individual disease and individual patient in 2020.

This approach was partly followed by James Mills (Pfizer Global R&D; http://www.pfizer.com) who, in addition, provided some hands-on knowledge of different target classes, such as the selectivity issue with kinase inhibitors, which often – rather unselectively – target ATP binding sites.

Screening for building blocks

Fragment-based screening is often fruitful in combination with NMR techniques, and this approach has been developed over the past couple of years. After having identified weak binding fragments, they can be linked to find a strongly binding ligand or alternatively, the molecule can be grown, to give a potent lead compound. Also amenable to X-ray techniques, fragment-based screening was presented by David Rees of Astex Technology (http://www.astex-technology.com), a company that was also involved in solving the X-ray structure of the cytochrome P450, CYP3A4, in 2002. Using what he called 'wet screening', they are capable of screening 500–1000 fragments at the same time in 'crystal soaking' experiments, a procedure that has already produced novel lead compounds against a range of kinases and proteases.

The ADME–Tox issue

Binding to a receptor is important in the first steps of drug discovery, but at a later stage of drug development the focus also needs to be on ADME properties of the potential drug. This is where *in silico* predictions come into play, which are, in principle, able to filter out compounds with undesired properties before clinical stages. Mike Tarbit (currently at ArQule UK; http://www.arqule.com) presented software that was developed to predict a wide range of drug properties – physicochemical properties like logP, but also blood–brain barrier penetration or CYP interactions. With an easy-to use interface, this software could be of some value for the medicinal chemist.

Where are we, and where are we heading?

As mentioned by several speakers, over the past few decades there has been a huge effort to 'rationalize' drug discovery, with the overwhelming majority of drugs on the market still being discovered –at least a good part – by pure chance. By combining bioinformatics methods in target selection, cheminformatics methods in the thorough selection of screening candidates and sophisticated (e.g. fragment-based) 'real-life' screening approaches, there is a good chance we will meet the common vision; that in 2020 we will have drugs that are tailored to both the individual disease and the individual patient.

References

1 Tufts Centre for the Study of Drug Development Outlook Report (2003). (available at: http://csdd.tufts.edu/)
2 Bolten, B.M. and DeGregorio, T. (2002) Trends in development cycles. *Nature Drug Discov.* 1, 335–336
3 Richards, W.G. (2002) Virtual screening using grid computing: The Screensaver Project. *Nature Drug Discov.* 1, 551–555
4 Glick, M. *et al*. (2002) Identification of ligand binding sites on proteins using a multi-scale approach. *J. Am. Chem. Soc.* 124, 2337–2344