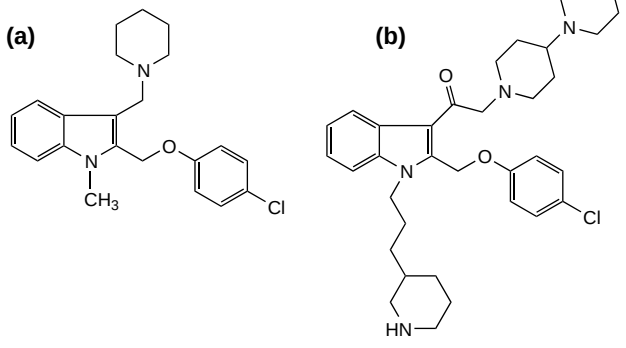

Figure 1. An example of potency led drug design. The original lead structure **(a)** appears to have excellent drug-like properties. As NPY Y-1 antagonist potency has been impressively increased **(b)** so oral drug properties have been attenuated.

would drive up the cost of delivering a development candidate out of discovery by a factor of 10–20. This is clearly not a sound business proposition. Moreover, ADME data is vital. Much of development candidate attrition is ADME-based and the new world demands that what begins as drug-like ends as a drug. The need for ADME property assessment is to ensure that the (oral) drug properties are maintained or produced as an early drug-like lead is advanced in potency by successive rounds of chemistry.

Figure 1 illustrates an example where this has not been done. The NPY Y-1 indole lead [3] would probably have good oral drug properties based on inspection of the structure, and its molecular weight (369), one measure of drug-like, complies with this. The resultant most potent compound of the series is 2000-fold more potent (around 1 nM) and this compound could be judged a great success on this single criteria. Unfortunately, it is now not a drug because it is unlikely to have good oral drug properties. As a measure of non drug-like, it has a molecular weight of 591 and also several positions of extreme metabolic vulnerability. When tested *in vivo*, the serum levels of the compound following oral administration were inadequate to evaluate the compound by this route [2]. So the cycles of parallel synthesis must be led by information on potency and selectivity against the pharmacological target and ADME properties. This is true SAR-led drug design or super-rational drug design; clearly differentiated from blind combinatorial chemistry or the single compound progression of traditional SAR-led rational drug design.

However, we have already established that conventional screening cannot stretch to providing the ADME information and guidance in a cost effective and timely manner, leaving the stage free for the *insilicoids* to rescue the 'real world'. The 'real world' needs 'them' like never before. The *insilicoids* have developed the inventory that Butina and colleagues have supplied. They now need to make the last tweaks to the software; to decide if it is 2D atom types, 3D atom–pair distances or polar surface area that are important; lock down on statistical regression, neural networks or genetic algorithms, and then come in force from *Insilico* and deliver in the new real world.

Whether it is pure *de novo in silico* or a partial use of screening information on selected subsets of each entire synthetic run, what is needed is a map of ADME space and target space to guide each cycle. The companies that succeed here will prosper; the companies that do not are at a disadvantage. Welcome *insilicoids* to the 'real world, real time zone'; get this right and do it now, and we'll make you the President.

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Patent opportunities in bioinformatics

Biotechnology research is a wide and diverse field of scientific endeavor that spans the study and development of transgenic organisms, the dissection of molecular and cellular pathways, pharmacogenomics and genetically modified crops. However, a common vein is seen to run through these varied areas of research, namely bioinformatics.

A reason that bioinformatics is needed in these fields is that many organisms have been the subject of intense genome sequencing. Scientists are faced with the task of converting this mountain of raw data into informative and useful information by discovering what portions of the data are useful and what portions are extraneous.

According to the National Institute of Health's (http://www.nih.gov) Biomedical Information Science and Technology Initiative Consortium, bioinformatics is generally defined as: 'Research, development or application of computational tools and approaches for expanding the use of biological, medical, behavioral or health data, including those to acquire, store, organize, archive, analyze or visualize such data.'

Although the classic term bioinformatics most often describes computerized technologies used to store,

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analyze and interpret biological data, the current, somewhat broader definition has come to encompass biomathematics (which can be described as the application of mathematical principles to biological processes). Population genetics, cellular biology, comparative genetics, pharmacokinetics, protein folding and cell membrane dynamics are fields of study in which mathematics is important. This also includes data mining (searching for comparative genomic data) and all other comparable techniques being developed to analyze and interpret the mountain of sequence data currently churned out at rates that are estimated to double the amount of available biological data every six months.

Sequence data provides the basic foundation for bioinformatics research. One example where an enormous amount of this 'raw' genetic data has been provided is the Human Genome Project. Biotechnology and pharmaceutical companies face the challenge of developing bioinformatics tools to transform this mass of information into valuable medical and therapeutic products.

Although the end products of genomics and proteomics studies (e.g. isolated compounds based upon sequences, both nucleic and amino acid) provide potentially patentable subject matter, in many cases the tools and techniques themselves will be as valuable – and in some cases more valuable – than the underlying biological data.

Accordingly, bioinformatic companies require the whole slew of various methods of protection afforded, such as intellectual property assets (copyright, trademark, trade secret and patents). Among these, patent protection will provide the main buttress that will support and reinforce a company's position in the marketplace, and in some cases even establishes the position of an organization.

Seeking patent protection for an improved technique or for a special apparatus is valuable both for offensive and defensive purposes. Defensively, research organizations can appreciate that being the first to patent a bioinformatics invention could prevent others from obtaining the same or similar patent that could block work by your organization. From an offensive standpoint, the allure of bioinformatics patents is the potential long-term economic value. Obtaining a patent for novel solutions to industry-specific difficulties provides research organizations with two primary paths to interact with other organizations.

First, if the other organization is a competitor, the patent owner could possibly enforce the patent to prevent the competitor from using the patented process, product or composition. This would give the patent owner an obvious competitive advantage until the competitor either developed its own solution to the problem or until the state of the art changed.

Second, and in many cases more appropriately, the patent owner can license the patented process or apparatus to anyone who might find it useful. The group of potential licensees might include others in the genomics field, as well as organizations in a variety of other fields. If the patent claims are properly drafted and sufficiently broad, they could cover many variations upon the particular process used by the patent owner, all of which could then be licensed.

Given the current and projected amount of capital to be invested in bioinformatics tools and services (US$40 billion over the next five years), companies and organizations that aggressively pursue patent protection for their bioinformatics inventions will be most likely to weather the extremely competitive and stormy milieu that has come to define the biotech marketplace.

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Blood hot in Boston

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Temperatures of 37°C plus warmed delegates in Boston (MA, USA) for the *5th International Biorelated Polymers Symposium* (at the 224th ACS National meeting, 18–22 August 2002); purportedly the hottest spell since the 1930s. This report is a snap shot of the meeting and will focus on some of the polymeric carrier technologies presented, which are specific to drug delivery and gene therapy.

Drug delivery

Immunoliposomes

The enhanced permeability and retention (EPR) effect is based on the non-specific penetration of particulate entities into the interstitium through leaky vasculature. Phosphatidylethanolamine-modified polyethylene glycol (PEG–PE) micelles are stable and long circulatory with dimensions that are ideally suited for exploiting the EPR opportunity. To explore this, Vladimir Torchilin (Northeastern University, http://www.northeastern.edu)

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