The Automation of Protein Expression

Through the integration of biology, instrumentation and an advanced information management system, a technology has been developed which fully automates protein expression – from gene to protein.

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From structural biologists to researchers developing assays and arrays, and raising antibodies, scientists increasingly require samples of protein for research. However, protein expression is considered to be a complex, lengthy procedure, and some proteins will not express at all. This article describes the strategy adopted by NextGen Sciences to develop and integrate software, instrumentation and biology to automate protein expression.

The production of proteins from DNA constructs for use in drug discovery is a major challenge facing scientists, and one of the major bottlenecks in protein research. A number of technologies have recently emerged in the protein research market to automate some of the molecular biology techniques involved in protein expression – such as systems for automated cloning, media enabling self-induction and fully automated cell culture systems. While these technologies are useful for alleviating some aspects of protein expression, individually they do little to remove the main hurdles – such as low protein yield, insolubility, high costs and time and resource commitments.

These difficulties are being faced across the protein research industry, and were experienced by NextGen Sciences as part of its programme of work to develop breast cancer biochips. Using conventional methods, the production of different proteins to meet the project’s demands presented a major hurdle. As a result, NextGen Sciences developed the ‘expressionfactory’ – the first commercially available technology to fully automate protein expression (see Figure 1).

FROM GENE TO PROTEIN AUTOMATICALLY

Through the integration of biology, instrumentation and an advanced information management system, NextGen Sciences developed a technology to fully automate protein expression, from gene to protein. Beginning with DNA species such as polymerase chain reaction (PCR) products, ORFs (open-reading frames) or cDNA libraries, the company designed the system to plan, automate and track the entire process of sub-cloning, expression and purification of hundreds of proteins in parallel.

Figure 2 illustrates some of the automated processes integrated by the expressionfactory, including molecular biology protocols in 96-well plate format, cell growth, expression induction, cell lysis, protein purification and refolding. Compatible with Gateway®, TOPO®, and traditional cloning techniques, the expressionfactory performs molecular biology processes in a seamless workflow.

Factors governing the success of expression include vector construction, and choice of fusion partners, host, and growth and induction conditions. However, it is extremely difficult for researchers to predict the combination of these factors required to optimise the expression of a protein, and certain proteins may require specific strategies to express at all. To address these difficulties, many researchers are...
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adopting a matrix approach to protein expression – involving the investigation of multiple combinations of expression possibilities in parallel. However, this approach is not without its own difficulties. Even with a single target sequence, the management of multiple combinations of constructs, vectors, hosts, conditions and so on quickly presents sample management and tracking problems. Furthermore, undertaking the laboratory work requires extensive time and resource commitments.

Rather than attempting different expression strategies one after the other in an iterative process, NextGen Sciences designed the expressionfactory to adopt a matrix approach to expression – to increase expression yield and improve the chances of successful expression.

The expressionfactory will insert genes, or multiple genes, of interest into a matrix of destination vectors simultaneously. Cell growth conditions and protein purification strategies may also be investigated – giving additional dimensions to the matrix. The system has the capacity to perform this research with many hundreds of genes of interest in parallel to identify the ‘best’ strategies for optimum expression of proteins in the desired form.

MANAGING INFORMATION

Due to the high numbers of proteins and different optimisation steps involved with the expressionfactory’s strategy for expression optimisation, there would quickly become sequence-, sample- and protein-tracking problems. To address these difficulties, NextGen Sciences developed a unique information management system – powered by LabVantage Sapphire™ – which the company calls OrchestratorIMS™.

The IMS creates location and activity logs for every sample, which makes it possible to define and track batch processes, such as PCR, cloning strategies such as Gateway® and purification. These logs are fed back into the system to ensure a complete audit trail is maintained from gene to protein. The user interface is a thin-web client, which means it can be reached through a browser on any computer connected to the LAN, either in the laboratory or in the office. Multiple researchers can therefore access the IMS, without the need to install the software on their PC.

The system has rules-based knowledge of molecular biology, which when combined with information from internal or external databases – GenBank for example – allows the researcher to design and execute virtual experiments, before committing biological materials in the lab.

OrchestratorIMS provides a link between experiments planned virtually and those performed manually in the laboratory. Once an experiment has been designed in the IMS, the protocol is sent to the instrument. The system then provides the user with a list of the biological materials, plates, tips and so on required to allow the run to begin.

DIFFERING THROUGHPUT NEEDS

The expressionfactory was launched by NextGen Sciences in 2003 and has since been purchased by major international pharmaceutical companies in the US and UK. Recently two new products have been introduced.

Following the launch of the expressionfactory, the company saw a lot of interest in the information management system behind the technology, and realised that it needed to provide customers with the software as a stand-alone product. The software enables users to plan their experiments at their PC, and then carry out their research using either manual techniques or laboratory robotics. The system generates detailed SOPs listing the laboratory work required, and will monitor and track the whereabouts of all biomaterials, samples and reagents.

The company has also launched the ‘expressionworkstation’, which integrates the OrchestratorIMS software with an optimised technology platform, and has disclosed that it will be introducing further new products for molecular biology and protein research before the end of 2004.

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