Editorial

AN UNCOMFORTABLE ALLIANCE?
Welcome to the third issue of Volume 1 of *Briefings in Functional Genomics and Proteomics*. Once again, we have tried to encompass a wide range of topics across a broad spectrum. There are contributions from both the private and public sectors, emphasising how narrow the divide is becoming between commercially and publicly funded efforts in terms of the scale and nature of research being carried out in these ‘high throughput’ fields. This, of course, is in part due to the size of some of the publicly funded efforts — cancer projects both in the USA (The Cancer Genome Anatomy Project; http://cgap.nci.nih.gov/) and the UK (The Cancer Genome Project; http://www.sanger.ac.uk/CGP/) leap immediately to mind, but there are many others. As a gradual shift in emphasis emerges, from sequencing to functional analysis, the large genome centres and institutes become obvious and natural hosts for functional genomics and proteomics programmes. Another factor may be that the academic community is working more closely not only with industry but also with suppliers of instruments, reagents and associated technology. Indeed, many companies now require that they are bedfellows in your research strategies. Microarray programmes provide a prime example of this, with the ‘supplier’ often holding the drawstrings on much of the technology being used: they will design your experiments for you in some cases and provide the optimal reagents based on their own (sometimes undisclosed) efforts. But this is not necessarily a bad thing and, in fact, allows the researcher from smaller groups to take more ambitious and expansive approaches to problem solving. It is basically a case of the supplier making bigger and bigger (and consequently more expensive) kits, never mind the fact that it also allows for more patent opportunities.

And so to the content of this issue. Having appraised the relative merits of protein–protein interactions using the yeast two-hybrid (Y2H) approach in issue 1, Norbert Lehming reviews an alternative approach, using the split ubiquitin system. While it is not perhaps as well suited to genome-wide screens for protein interactions, one of the potential advantages of this system is that it can access interactions in both the cytoplasm and the nucleus, whereas conventional Y2H approaches can only assay nuclear interactions. Moreover, the split ubiquitin system is not dependent on transcription of a gene product (as it is a direct protein complementation assay) and can, therefore, be used to analyse transcription factors, which generate false positives using the Y2H system.

Functional genomics approaches often rely on interfering with gene function at various levels. Sumanas and Larson review the use of morpholino oligonucleotides to analyse gene function, chiefly with zebrafish, allowing controlled and reproducible phenocopying of mutations in many different genes. This approach promises great things, including the potential of partial gene knockdown using low doses of morpholino. The authors are careful to point out that proper controls are essential in order to interpret the results of this kind of experiment correctly, an essential element of any experiment on complex, *in vivo* systems. Zebrafish are remarkably tractable organisms for this form of study — the development of transparent embryos can be visualised and monitored on a microscope slide and foreign material (DNA and RNA, for instance) may be relatively easily introduced at an early stage. It will be interesting to see how easily morpholino technology is transferred to other model organisms, and, in particular, to mammals.

In contrast to the gene knockdown strategies associated with morpholinos, Brenda Eustace and colleagues discuss the power of a protein knockdown approach using...
chromophore-assisted laser inactivation (CALI). This technique allows spatial and temporal inactivation of antibody-bound protein targets using laser irradiation of a malachite green conjugate. This exciting technology has the capability of single cell resolution and is currently being adapted to more high throughput approaches. As with most fluorescence-based techniques, the use of an increasing repertoire of dyes promises greater flexibility and the ability to inactivate multiple targets simultaneously.

While the number of genes predicted in vertebrate genomes has come down in the past few years, the degree and complexity of alternative splicing appears to be greater than first thought. Louise Woodley and Juan Valcárcel review comprehensively the current understanding of how splicing is regulated. Understanding how alternate splicing is regulated should allow us to predict which of the numerous potential splice forms that each gene can generate actually results in a mature, biologically relevant product. It seems that we have some way to go in our comprehension of these splicing rules, but, in the meantime, extensive cataloguing of identified alternate transcripts, from expressed sequence tag and complementary DNA databases, remains a valuable process.

With its genome reaching draft status, the mouse strengthens its position as the most widely used animal in laboratory research, particularly when applied to understanding the molecular basis for genetic disease and, consequently, drug development. Generating and maintaining mouse models of human diseases can, nevertheless, be very costly and, as a consequence, large programmes exist which combine a non-targeted approach to generate random, and usually point, mutations with extensive phenotyping processes. Pat Nolan reviews the use of ENU mutagenesis in the mouse with particular emphasis on its application to human genetic disease. He also provides a comprehensive listing of sources of additional information and resources. As well as phenotyping, Nolan discusses genotype-driven approaches to mutation generation and detection, using suitably archived DNA samples. Finally, he looks at ways in which mutagenesis models may be used to dissect polygenic disorders.

The complex world of obesity presents us with a number of polygenic conundrums. In our final article, Ben Challis and Giles Yeo discuss past, present and future strategies in the quest to dissect the intricacies of body weight regulation. Mouse models have been instrumental in a great deal of the research in this area and mutagenesis programs, such as those described by Pat Nolan, will surely play a major part in accelerating the elucidation of some of the genetic pathways involved. However, new technologies are increasingly featuring in the obesity battle and the authors review the impact that they are having on this increasingly common modern condition.

It is exciting to see how new technologies are keeping pace with, and helping to further, our understanding of how the genome and the proteome functions. We are still at the developmental stage in these new challenges, but at least we are arming ourselves with the tools to make the task appear a little more realistic.

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